Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

APRIL--1958

Volume 8 — Number 4

'Thorazine' Spansule capsules are excellent for the discharged mental patient

'Thorazine' *Spansule* capsules provide all-day maintenance therapy with a single dose taken in the morning. Discharged patients are saved the embarrassment of taking medicine at work, and the risk of forgotten midday doses is eliminated.

Most important of all, the continuous medication provided by 'Thorazine' *Spansule* capsules helps the discharged patient deal with the stress situations he encounters so frequently during his rehabilitation.

'Thorazine' *Spansule* capsules are offered in four strengths: 30 mg., 75 mg., 150 mg. and 200 mg.

THORAZINE* chlorpromazine, S.K.F.

SPANSULE* sustained release capsules, S.K.F.

Smith Kline & French Laboratories, Philadelphia 1

first ⧗ in sustained release oral medication

*T.M. Reg. U.S. Pat. Off.

in
Parkinson's
disease

PANPARNIT

(caramiphen hydrochloride GEIGY)

helps
your
patients
resume
a
more
normal
life

By relieving muscular rigidity and, in many patients, reducing tremor, PANPARNIT increases freedom and ease of movement. Gait is improved and parkinsonian patients are better able to feed, dress, and care for themselves. PANPARNIT seldom produces the disturbances of vision and dryness of mouth characteristic of belladonna derivatives.

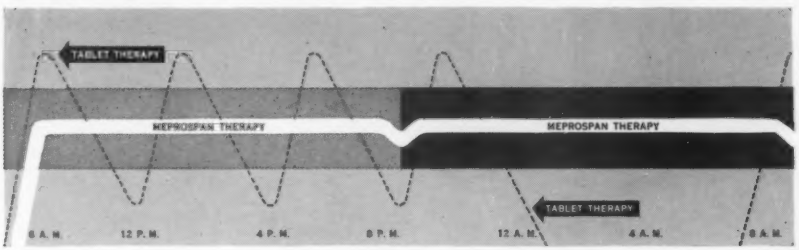
PANPARNIT® (caramiphen hydrochloride GEIGY): Sugar-coated tablets of 12.5 mg. and 50 mg.

GEIGY

Ardsley, New York

New... meprobamate prolonged release capsules

Evenly sustain relaxation of mind and muscle 'round the clock



TWO MEPROSPAN CAPSULES IN THE MORNING
RELIEVE ANXIETY, TENSION AND SKELETAL MUSCLE SPASM THROUGHOUT THE DAY.

TWO MEPROSPAN CAPSULES AT BEDTIME
PROVIDE UNINTERRUPTED SLEEP THROUGHOUT THE NIGHT.

Meprospan*

MEPROBAMATE IN **PROLONGED RELEASE** CAPSULES

- maintains constant level of relaxation
- minimizes the possibility of side effects
- simplifies patient's dosage schedule

Dosage: Two Meprospan capsules q. 12 h.
Supplied: Bottles of 30 capsules.
Each capsule contains:
Meprobamate (Wallace) .....200 mg.
2-methyl-2-n-propyl-1,3-propanediol dicarbamate

Literature and samples on request.

*TRADE-MARK CME-6598-48

WALLACE LABORATORIES, *New Brunswick, N. J.*

Volume 8 **Neurology** *Number 4*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

FRANCIS M. FORSTER, M.D., *President*

AUGUSTUS S. ROSE, M.D., *President-Elect*

A. L. SAHS, M.D., *Vice-President*

JOSEPH M. FOLEY, M.D., *Secretary*

CHARLES VAN BUSKIRK, M.D., *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*

Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*

Editorial Board: PEARCE BAILEY, M.D., *Washington, D. C.*

JOE R. BROWN, M.D., *Rochester, Minnesota*

ROLAND P. MACKAY, M.D., *Chicago, Illinois*

H. HOUSTON MERRITT, M.D., *New York, New York*

JAMES L. O'LEARY, M.D., *St. Louis, Missouri*

E. P. RICHARDSON, JR., M.D., *Boston, Massachusetts*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

J. PRESTON ROBB, M.D., *Montreal, Canada*

DONALD B. TOWER, M.D., *Bethesda, Maryland*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

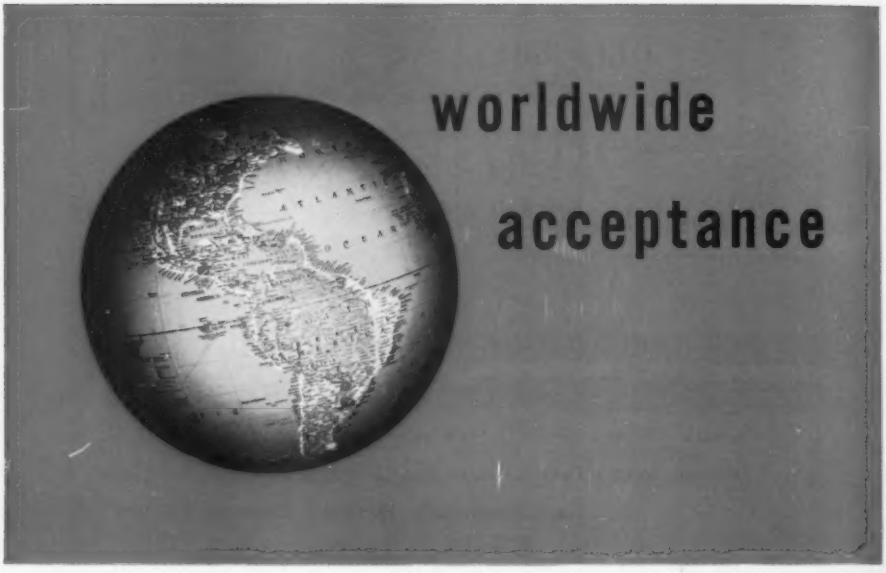
PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

"MYSOLINE"®

Brand of Primidone

in epilepsy



Reports from 15 countries attest to the clinical effectiveness of "Mysoline" in grand mal and psychomotor attacks. These results are confirmed by three years of successful use in the United States. No irreversible toxic effects have been reported. When side effects such as drowsiness and ataxia occur, they are usually mild and transitory, tending to disappear as therapy is continued or dosage is adjusted.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Ayerst

AYERST LABORATORIES • NEW YORK, N. Y. • MONTREAL, CANADA

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries Ltd.

5760

Volume 8 **Neurology** *Number 4*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

APRIL 1958 • *Contents*

The Neuropathies of Diabetes 243
JOHN F. SULLIVAN, M.D.

Uncinate Fits 250
DAVID DALY, M.D.

Unusual Form of Cerebellar Ataxia with Sex-Linked Inheritance 261
NATHAN MALAMUD, M.D. AND PETER COHEN, M.D.

Effect of Methylphenidate Hydrochloride in Antagonizing Barbiturate-Induced Depressions 267
HOWARD TICKTIN, M.D., JEROME EPSTEIN, M.D., JAMES G. SHEA, M.D. AND JOSEPH F. FAZEKAS, M.D.

Distribution of Cutaneous Hyperalgesia 272
GERALD H. KLINGON, M.D. AND WILLIAM H. JEFFREYS, M.D.

Cerebral Hemispheric Tumors and Extrapyramidal Signs and Symptoms 277
RICHARD L. ROTH, M.D. AND JOSE BEBIN, M.D., Ph.D.

Progressive Demyelinating Leukoencephalopathy 285
FREDERICK J. WOHLWILL, M.D. AND RICHMOND S. PAINE, M.D.

Demonstration of Carotid Occlusion by Small Dose Arteriography 296
W. H. OLDENDORF, M.D.

Free Amino Acid Content of Cerebrospinal Fluid in Humans and Dogs 299
JOHN LOGOTHETIS, M.D.

(Continued on next page)

NEUROLOGY, copyright 1958 by LANCET PUBLICATIONS, INCORPORATED. Title registered United States Patent Office. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. 84 S. Tenth St., Minneapolis 3, Minn. ADVERTISING REPRESENTATIVES: *New York 17:* Lee Klemmer, Bernard A. Smiler, John Winter, 1 E. 42nd St. Telephone: Murray Hill 2-8717. *Chicago 6:* Jay H. Herz, Hugh Gibson, 20 N. Wacker Drive, Suite 1921. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., Mills Bldg. Telephone: Garfield 1-7950. *Los Angeles 57:* Duncan A. Scott & Co., 1901 West Eighth St. Telephone: Dunkirk 8-4151.

Contents — *Continued*

Editorial 303
FRANCIS M. FORSTER, M.D.

Case Reports

Progressive Dystrophy of the External Eye Muscles 304
WALTER R. KIRSCHBAUM, M.D. AND JOHN J. HOLLAND, M.D.

Paralysis of the Dorsal Interosseous Nerve Not Due to Direct Trauma—A Case Showing Spontaneous Recovery 307
FRANCIS KRUSE, JR., M.D.

Book Reviews 309

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D.C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

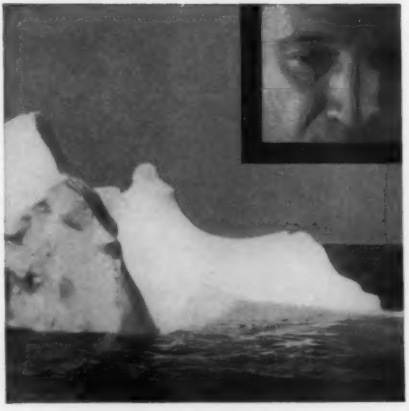
Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 3. Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

WHEN A MAN
IS MENTALLY
AN ICEBERG
RESTORE
EMOTIONAL
WARMTH



The schizophrenic's cold, rigid and irrational emotional tone melts away as Pacatal restores emotional warmth. Lack of responsiveness is one of the many symptoms which Pacatal corrects by normalizing thinking and emotional patterns. Many investigators report a return of warmth and improved affect.[1,2,3]

PACATAL...

- "normalizes" thinking and emotional responses
- calms without "flattening"—keeps patients alert
- elevates the mood instead of sedating the patient

complete literature available on request

References
1. Flipse, M. J.: Clin. Med. 4:1237 (Oct.) 1957. 2. Hutchinson, J. T.: Paper presented, American Psychiatric Association, Philadelphia, Pa., Nov. 17, 1956. 3. Sarwer-Foner, G. J., and Koranyi, E. K.: Canad. M. A. J. 77:450 (Sept. 1) 1957.

FOR NORMALIZATION—NOT SEDATION

Pacatal®

BRAND OF MEPAZINE

WARNER-CHILCOTT

to control tranquilizer-induced Parkinson-like side effects

COGENTIN®

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

'COGENTIN' is effective in providing relief for many patients who develop tremor, restlessness, feelings of tension and other Parkinson-like symptoms during tranquilizer treatment of mental disorders.

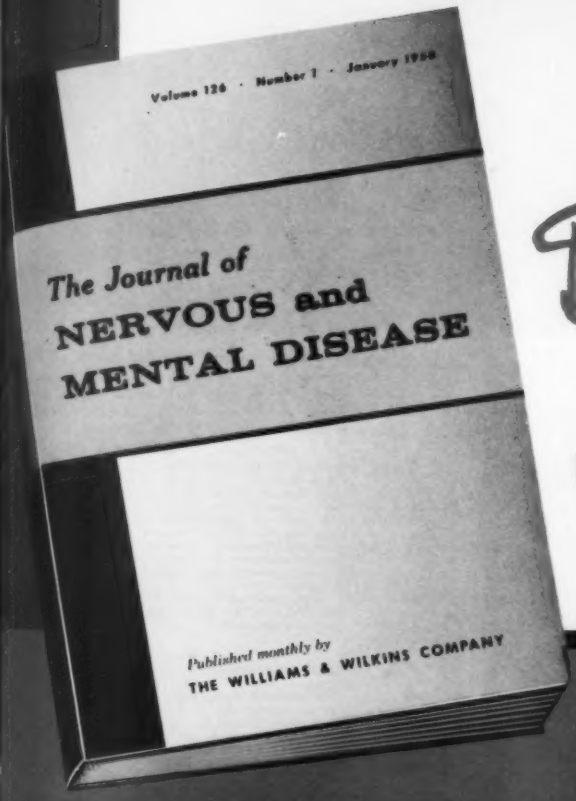
DOSAGE AND ADMINISTRATION: Recommended dosage is one-half to one tablet two or three times a day. If higher doses are required, the patient should be closely observed and dosage adjusted as indicated. When 'COGENTIN' is used to offset the distressing Parkinson-like side effects caused by tranquilizing drugs, adequate therapy with these drugs may usually be continued. Rarely, a decrease in dosage may be necessary.

SUPPLIED: As 2 mg. quarterscored tablets in bottles of 100 and 1000.

COGENTIN is a trade-mark of Merck & Co., Inc.

MSD MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

THE INTERDISCIPLINARY APPROACH...



A New Dimension IN THE LITERATURE

"Each specialist reflects his own experience and is usually convinced of the correctness and usefulness of his own point of view in understanding the ground rules of discovery and experiment. For productive work it is not only necessary to grope for a unifying theory, it is also necessary to tie together into a working and productive unit those who specialize in a broad array of disciplines from mathematics to philosophy including biochemistry, psychology, sociology and anthropology."

JACOB E. FINESINGER, Editor,
J. Nerv. and Ment. Dis.,
Vol. 126,
No. 1

Aims and Scope

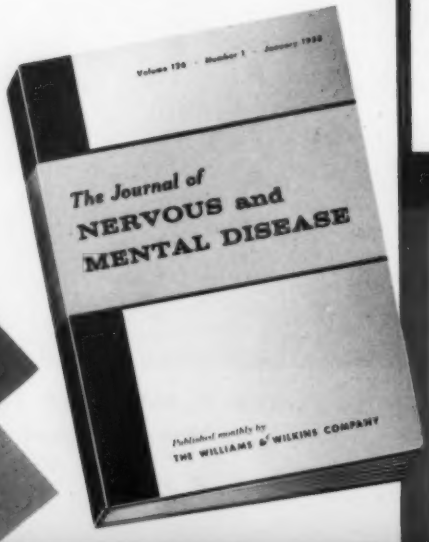
From the time of its first appearance as the **Chicago Journal of Nervous and Mental Disease** in 1874, the editorial policy has been sensitive to the new and promising.

Now under the editorship of Dr. Jacob E. Finesinger, the **Journal of Nervous and Mental Disease** will continue in this tradition to bring to practitioners of neurology and psychiatry, and to investigators in the fields of biology and medicine, scientifically sound and clinically useful material.

THE INTERDISCIPLINARY APPROACH

Appropriately, the journal will be edited at The Psychiatric Institute of the University of Maryland School of Medicine, a research, training and teaching institute that aptly reflects an interprofessional approach to the study of human behavior.

Editorial and Advisory



DR. JACOB E. FINESINGER
Editor-in-Chief
The Psychiatric Institute, U. of Md.
Professor of Psychiatry and Director of The Psychiatric Institute since its founding 1952. Author of some seventy papers on cerebral circulation, conditioned reflexes, autonomic nervous system, respiration, and endocrine studies in psychiatric disturbances. Clinical studies include psychiatric factors in atopic dermatitis, peptic ulcer, essential hypertension and fatigue. Particularly active in studying and developing methods and aids in teaching psychiatry.

DR. H. A. ROBINSON
Managing Editor
The Psychiatric Institute, U. of Md.
Associate Professor of Psychiatry, The Psychiatric Institute. Has been on faculty of Harvard and Yale Universities. Published in the fields of rehabilitation, adjustment to disability, sociology and clinical psychology.

DR. ROBERT G. GRENELL
Associate Editor
The Psychiatric Institute, U. of Md.
Professor of Psychiatric Research, The Psychiatric Institute. Formerly on faculty of University of Minnesota and at Yale; formerly Fellow of U.S. Public Health Service, Johnson Foundation for Research in Medical Physics, University of Pennsylvania, and at Jenkins Department of Biophysics, The Johns Hopkins University. Major publications in neurophysiology and neurochemistry.

ADVISORY BOARD

DR. RAYMOND D. ADAMS
Boston
DR. W. ROSS ASHBY
Gloucester, England
DR. PHILIP BARD
Baltimore
DR. MANFRED BLEULER
Burgholzli, Switzerland
DR. MARY A. B. BRAZIER
Boston
DR. JEAN DELAY
Paris
DR. JOEL ELKES
Bethesda
DR. ANGEL GARMA
Buenos Aires
DR. WENDELL R. GARNER
Baltimore
DR. MARIO GOZZANO
Rome
DR. MANFRED S. GUTTMA
Baltimore
DR. D. O. HEBB
Baltimore
DR. ERNEST R. HILGARD
Stanford
DR. HANS HOFF
Vienna
DR. MAXWELL JONES
Sutton, England
DR. MAURICE LEVINE
Cincinnati
DR. NOLAN D. C. LEWIS
Princeton
DR. A. H. MASLOW
Waltham

To do this the **Journal** will present and encourage a multidisciplinary approach. That is, in addition to publishing specific studies in such fields as psychiatry, neurology, neurophysiology, clinical psychology, sociology, and biochemistry, the **Journal** will integrate these various disciplines. It will emphasize investigations that cross boundaries between professions that are relevant to the practitioner and his work. In short, it will help the physician to develop a broad conceptual framework by which he can better understand his patient.

Thus broadly conceived, the **Journal** will meet the challenge of our times, when new ideas and discoveries primarily in the behavioral sciences are forcing us to re-evaluate our concepts of behavior.

You are invited now to subscribe to the **Journal of Nervous and Mental Disease** on the convenient terms stated on the order card.

The newly formed Editorial Board of the Journal has been selected on an interdisciplinary basis. Each member has made significant contributions beyond the boundaries of his own profession.

DR. ROBERT A. CLEGHORN
Psychosomatic Medicine
Allan Memorial Institute of Psychiatry
Director of Laboratory for Experimental Therapeutics, Allan Institute, Montreal; Associate Professor of Psychology and Lecturer in Medicine, McGill University. Member of the editorial or advisory board of six professional journals. Chief fields of research include psychosomatic medicine, clinical endocrinology, carbohydrate metabolism. Member of Committee on Research, American Psychiatric Association.

DR. JAMES L. O'LEARY
Neurology
Washington University School of Medicine
Professor of Neurology at Washington University, St. Louis, where he has held teaching positions for twenty-five years. He has published approximately one hundred scientific articles, largely in neurological areas.

DR. JEROME D. FRANK
Psychiatry - Group Therapy
Henry Phipps Psychiatric Clinic
Associate Professor of Psychiatry, Johns Hopkins. Has written chiefly on psychotherapy and group psychotherapy. Chairman of the Committee on Medical Education, Group for the Advancement of Psychiatry; Chairman of Committee on Research, American Group Psychotherapy Association.

DR. TALCOTT PARSONS
Behavioral Science
Harvard University
Professor of Sociology and Chairman, Department of Social Relations, Harvard University. Received a Ph.D. from Heidelberg in 1927, and holds a number of honorary degrees. Has written widely in areas of social and economic theory and social institutions. His writings include: **Structure of Social Actions, The Social System, Essays in Sociological Theory.**

DR. ROBERT R. HOLT
Behavioral Science
Research Center for Mental Health, N.Y.U.
Associate Professor of Psychology, Director of Research Center for Mental Health, Graduate School of Arts and Sciences, New York University. Has taught at Harvard, the Menninger Foundation, and University of Kansas. An active consultant to various scientific organizations, and is an editor of a number of professional journals.

DR. THOMAS S. SZASZ
Psychoanalysis
State University of New York
Professor of Psychiatry, State University of New York, Syracuse. Born in Budapest, he came to the U. S. in 1938 and received his M.D. from University of Cincinnati. A practicing psychoanalyst, Dr. Szasz has published widely in psychiatry and psychoanalysis, as well as psychosomatic medicine. His book **Pain and Pleasure** was published by Basic Books in 1957.

Postage Will be Paid by Addressee

No Postage Stamp Necessary If Mailed in the United States

BUSINESS REPLY CARD
First Class Permit No. 724, Baltimore, Maryland

THE WILLIAMS & WILKINS COMPANY
Medical and Scientific Publishers
Mount Royal and Guilford Avenues
Baltimore 2, Maryland

A Preview

THE INTERDISCIPLINARY APPROACH . . .

Outstanding articles in the January, 1958, issue of the JOURNAL OF NERVOUS AND MENTAL DISEASE

THE NATURE OF APRAXIA

By D. Denny-Brown

One of our foremost clinicians brings together problems of neurology and psychology. Distinguishes between ideational and kinetic apraxia on the basis that the former is related to non-physiological aspects of behavior.

ON THE PARTICIPATION OF ADAPTIVE HORMONES IN DISEASE SUSCEPTIBILITY

By Hans Selye

The most recent contribution to the field of adaptability to stress by a pioneer in that important area.

THE SEVERELY DEFECTIVE INDIVIDUAL

By Seymour B. Sarason and Thomas Gladwin

A psychologist and anthropologist explore the relationship between psychoses and subnormal functioning. The first intensive study of this important area.

SOME ASPECTS OF AMINO ACID AND PROTEIN METABOLISM OF THE NERVOUS SYSTEM

By Dr. Heinrich Waelsch

Deals with metabolism of nitrogenous compounds in the central nervous system. Of primary interest not only because of the role of amino acids in the formation of proteins and active amines (such as noradrenalin, seratonin, etc.), but also because of their possible major activity in the mechanisms of storage and transmission of information.

A CATARACT OF CONSEQUENCES

By Alan Gregg

Read at the Dedication of the Psychiatric Institute, University of Maryland School of Medicine, Baltimore, 1952. This previously unpublished manuscript by Dr. Gregg is particularly appropriate to the inauguration of the new editorial policy of the Journal, in that it clearly reflects the multi-disciplinary point of view of this great educator.

Important papers read before the 1957 meeting of the Society of Biological Psychiatry . . .

Visceral Brain, Its Component Parts and Their Connections.

By James W. Papes

Effects of Septal and Amygdaloid Lesions on Emotional Behavior and Conditioned Avoidance Responses in the Rat.

By Frederick A. King.

Read this trial subscription offer carefully

THE WILLIAMS & WILKINS COMPANY • BALTIMORE

Enter my subscription to Journal of Nervous and Mental Disease on the following basis:

- ☐ Send me at once the January issue and include your invoice for 1958 with it. After I have read the first issue I will return one copy of your bill together with the full subscription price for 1958 ($15.00, U. S.; $15.50, Canada; $16.50, all other countries). If I wish to receive the rest of this year's numbers. Otherwise, I agree to return your invoice marked "Cancel." In any event, I need not return the first issue.
- ☐ Full payment is enclosed ($15.00, U. S.; $15.50, Canada; $16.50, all other countries).
- ☐ I am already a subscriber. Payment is enclosed—extend my subscription for another year.

Name _____ (Please Print)

Street and No. _____

City _____ Zone _____ State _____

I specialize in _____

ARD IS PERFORATED—TEAR ALONG DOTTED LINE

JOURNAL OF NERVOUS AND MENTAL DISEASE

Volumes 126-127
Current in 1958
Subscription price per year:
$15.00 U. S.
$15.50 Canada
$16.50 all other countries

This subscription order card requires no postage. Subscribe Now!

now available
the **parenteral** form
Trilafon® Injection
perphenazine

full-range tranquilizer
potent antiemetic

effective prevention and emergency control of severe nausea and vomiting in surgery and obstetrical cases; highly agitated mental states

virtually free from significant hypotension and pain on injection

no apparent impairment of mental acuity

TRILAFON Injection—5 mg., ampul of 1 cc., boxes of 6 and 100.

Refer to Schering literature for specific information regarding indications, dosage, side effects, precautions and contraindications.

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

TR-J-118

REVIEW COURSES IN
BASIC and CLINICAL NEUROLOGY

APRIL 21, 22, 23, 1958

Preceding the

1958 AMERICAN ACADEMY OF NEUROLOGY MEETING

Bellevue-Stratford Hotel, Philadelphia, Pennsylvania

NEUROPATHOLOGY—April 21, 1958. Dr. Erland R. Nelson. Fees: Juniors $15.00; Fellows, Actives, and Associates: $20.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

DISORDERS OF MOVEMENT—April 21, 1958. Dr. Charles A. Kane. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEUROPHARMACOLOGY—April 21, 1958. Dr. Donald B. Tower. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

ELECTROENCEPHALOGRAPHY—April 22, 1958. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

PEDIATRIC NEUROLOGY—April 22, 1958. Dr. Sidney Carter. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

PHYSIOLOGY AND DISEASES OF CEREBRAL CIRCULATION—April 22, 1958. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

CURRENT ADVANCES IN NEUROLOGY—April 23, 1958. Dr. Joe R. Brown. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEURO-OPHTHALMOLOGY—April 23, 1958. Dr. N. S. Schlezinger. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

FINE STRUCTURE OF THE NERVOUS SYSTEM—April 23, 1958. Dr. William F. Windle. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

ENROLLMENT FOR ALL COURSES IS LIMITED
Priority will be determined by date of application
No application will be accepted after April 1, 1958

•

Outline of each course, application and further information may be obtained from

Mrs. J. C. McKinley, Executive Secretary
3501 East 54th St., Minneapolis 17, Minnesota

UNIQUE Robins ***research discovery***

for SELECTIVE, SUPERIOR

skeletal muscle relaxation

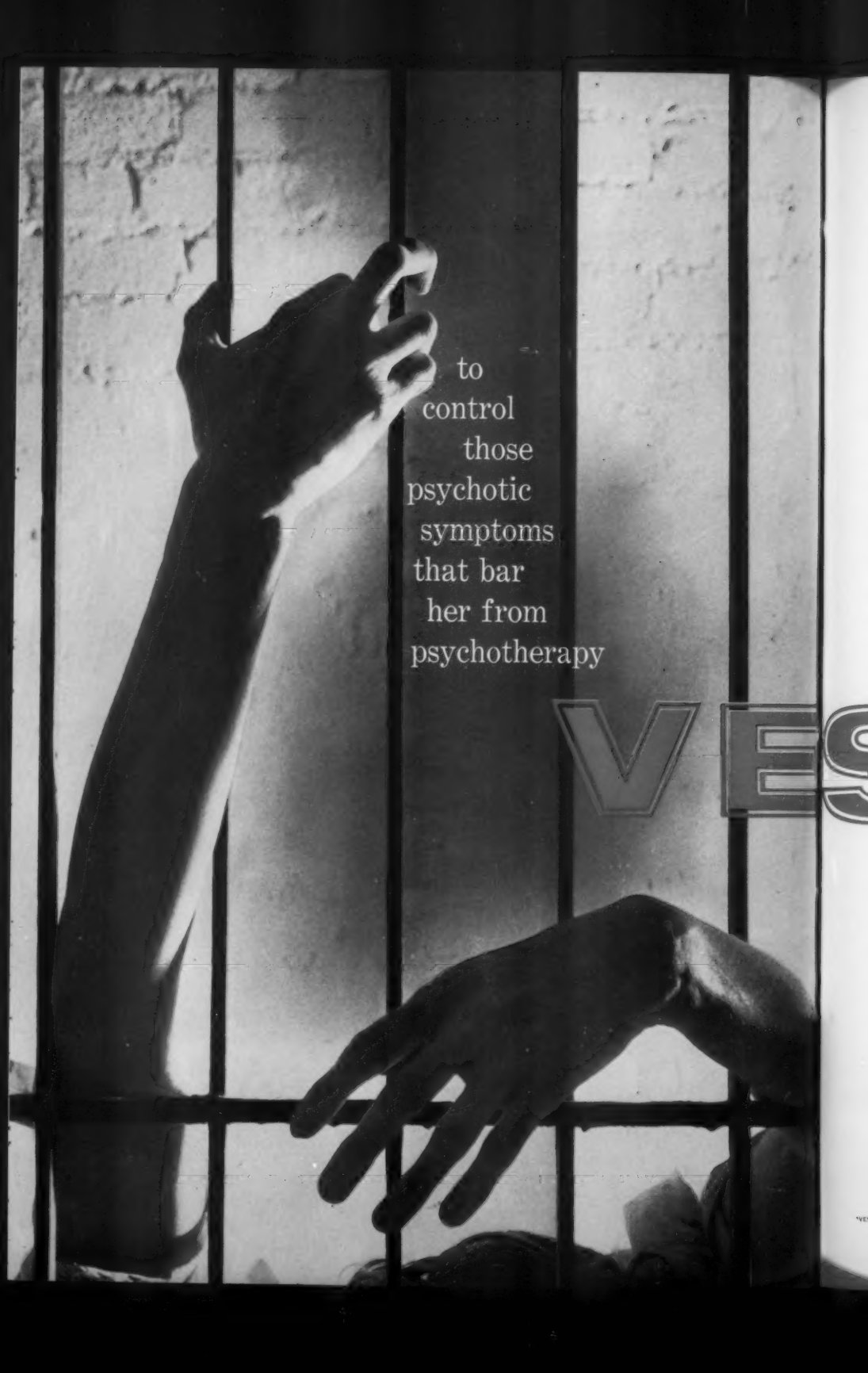
ROBAXIN—a completely new chemical formulation—provides sustained relaxation of skeletal muscle spasm, without impairment of muscle strength or normal neuromuscular function . . . and with essential freedom from adverse side effects. Beneficial in 94.4% of cases tested.

Robaxin®

METHOCARBAMOL "ROBINS", U.S. PAT. NO. 2,770,641

Supply:
Tablets, 0.5 Gm., bottles of 50.

A. H. ROBINS CO., INC., *Richmond 20, Virginia*
Ethical Pharmaceuticals of Merit since 1878


to
control
those
psychotic
symptoms
that bar
her from
psychotherapy
VES

CHEMICALLY IMPROVED — beneficial properties potentiated . . . unwanted effects reduced, through modification of the phenothiazine structure

PHARMACOLOGICALLY IMPROVED — enhanced potency with far less sedative effect

CLINICALLY IMPROVED — does not oversedate the patient into sleepiness, apathy, lethargy . . . active and rapid in controlling manic excitement, psychotic agitation and panic, delusions and hallucinations, hostility, and intractable behavior . . . drug-induced agitation minimal

AND IN EXTENSIVE CLINICAL EXPERIENCE — SINGULARLY FREE FROM TOXICITY

■ jaundice or liver damage—not observed ■ skin eruptions—rare ■ photosensitivity—rare ■ hyperthermia—rare ■ convulsions—not observed

IN SCHIZOPHRENIA / MANIC STATES / PSYCHOSES ASSOCIATED WITH ORGANIC BRAIN DISEASE

effects smooth and rapid control of psychotic symptoms ⟶ facilitates insight ⟶ permits early introduction of psychotherapy ⟶ improves patient-personnel relationship ⟶ hastens social rehabilitation

SPRIN

Squibb Trifluprom**azine** Hydrochloride

the new, improved agent for better management of the psychotic patient . . . with greater freedom from toxicity

DOSAGE:

Oral route—usual initial dosage, 25 mg., t.i.d. Adjust dosage according to patient response. (Observe caution in giving daily oral doses in excess of 300 mg.)

Intramuscular route—suggested dosage, 20 mg., t.i.d. (Observe caution in exceeding daily intramuscular doses of 150 mg.)

(See package insert for additional information)

Oral Tablets: 10 mg., 25 mg., 50 mg. press-coated tablets in bottles of 50 and 500

Parenteral Solution: 1 cc. ampuls (20 mg./cc.)

"VESPRIN" IS A SQUIBB TRADEMARK

SQUIBB *Squibb Quality—The Priceless Ingredient*

"Doctors can't help shingles?"

Physicians who have used PROTAMIDE extensively deplore such statements as unfortunate when they appear in the lay press. They have repeatedly observed in their practice quick relief of pain, even in severe cases, shortened duration of lesions, and greatly lowered incidence of postherpetic neuralgia when PROTAMIDE was started promptly. A folio of reprints is available. These papers report on zoster in the elderly—the severely painful cases—patients with extensive lesions. PROTAMIDE users know "shingles" *can* be helped.

PROTAMIDE®

Sherman Laboratories

Detroit 11, Michigan

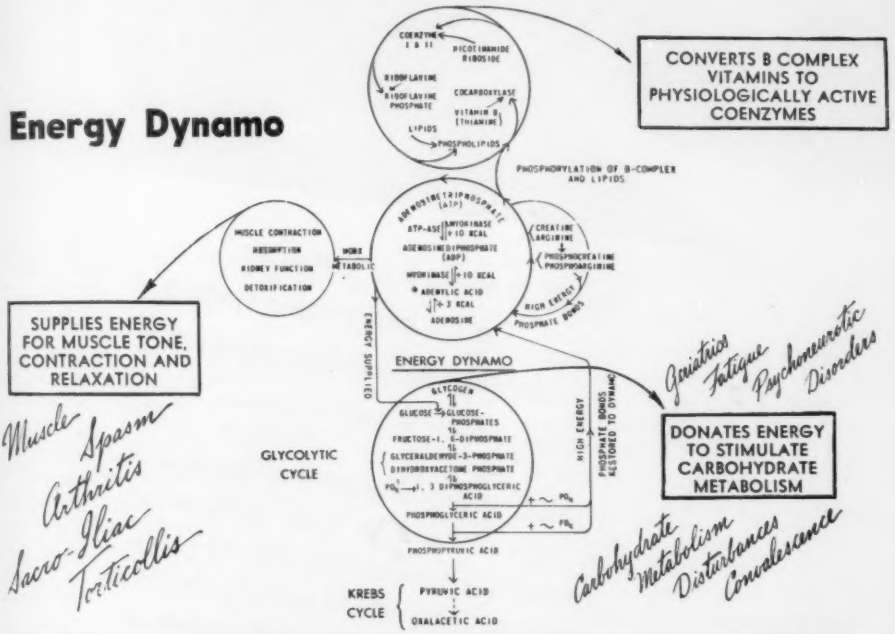
Available: Boxes of 10 ampuls—prescription pharmacies.

IRONYL®

The Iron Salt of **Adenosine-3-Monophosphate**

THE ROLE OF THE ADENYLIC SYSTEM IN ENERGY EXCHANGES GOVERNING PHYSIOLOGICAL PROCESSES

Energy Dynamo



CLINICALLY: IRONYL, THE IRON SALT OF ADENYLIC ACID, IS AVAILABLE IN ONE CC. AMPULS AND SUBLINGUAL TABLETS.

Gradually the role of the enzyme ADENYLIC ACID in clinical medicine is being clarified, leading to applications in an expanding number of indications, particularly where there are disturbances in the metabolism of muscle energy, and in diseases where there is an early breakdown of nerve or muscle cells.

IRONYL is indicated in the treatment of diseases associated with spasm, insufficient relaxation and lack of muscle tone in striated muscles, in B complex therapy, fatigue and exhaustion.

IRONYL IS SUPPLIED IN BOXES OF 10, 25, 100 AMPULS AND 12, 25, AND 250 TABLETS

PHYSIOLOGICAL CHEMICALS COMPANY, Inc.
New Rochelle, N. Y.

AVAILABLE ON REQUEST an annotated Bibliography, "ABSTRACTS ON THE ADENYLIC NUCLEOTIDES" with particular reference to Yeast Adenylic Acid (Adenosine-3-Monophosphate).

(In writing to advertisers, please mention NEUROLOGY)

"Anxiety, in one form or another, is the most common symptom confronting the practicing physician"[1]

1. Hollister, L.H., et al.: Dis. Nerv. System 17:289 (Sept.) 1956.

Whether anxiety is primary or secondary to organic illness, it is an obstacle to successful treatment. EQUANIL alleviates stress reactions; reduces anxiety, tension, and insomnia, and thus contributes to total patient management. Of all ataractic drugs, EQUANIL has the broadest usage in the common problems of everyday practice.

anxiety is the voice of stress

EQUANIL
Meprobamate
PHENERGAN® HCl
Promethazine HCl
SPARINE® HCl
Promazine HCl

A Wyeth normotropic drug for nearly every patient under stress

Wyeth®
Philadelphia 1, Pa.

Equanil
Meprobamate

Relieves tension—mental and muscular

Neurology Volume 8 • Number 4

The neuropathies of diabetes

John F. Sullivan, M.D.

THIS PAPER proposes to demonstrate by clinical means that diabetic neuropathy assumes two distinct forms: one, a classic symmetric distal neuropathy; the other, an asymmetric, predominantly motor neuropathy or radiculopathy. It seems a reasonable hypothesis that these two syndromes are clinically, and presumably pathologically, different entities, with contrasting onset and prognosis (table 1). Furthermore, it is possible to demonstrate that the asymmetric motor neuropathy, in particular, may antedate the clinical evidence of diabetes, thus indicating that diabetes in latent form is exerting its influence before fasting hyperglycemia and glycosuria alert the physician to the diagnosis.

For the purpose of clarity, it seems best to designate these syndromes as the "symmetric distal" and the "asymmetric motor" neuropathies. There is a temptation to refer to the symmetric distal neuropathy as the symmetric sensory neuropathy to emphasize the contrast and to indicate that it is predominantly sensory, but occasionally weakness is the presenting and outstanding feature. A third designation is that of a "mixed neuropathy," which indicates that both syndromes may be present simultaneously.

The observations in this report are based upon a study of patients admitted to the neurology service of a university hospital. For some years we have been interested in the neurologic complications of diabetes mellitus, because our experience has differed somewhat from that of others, as reflected in current textbooks and much of the medical literature on the subject. Forty-two cases of diabetic neuropathy form the basis of this study.

SYMMETRIC DISTAL NEUROPATHY

This is the classic syndrome and is recognized as such by the average physician. Eleven of our 42 cases had a symmetric distal neuropathy and six had both a symmetric distal and an asymmetric motor neuropathy. Fifteen of these 17 patients were known to have diabetes mellitus before entering the hospital (table 2).

The symmetric distal neuropathy is insidious in onset and is predominantly sensory. It may remain mild and non-incapacitating, but in chronic or uncontrolled diabetes, increasing disability may develop, with weakness, trophic changes, painless bladder distension and atony, impotence, and nocturnal diarrhea. Pupillary abnormalities simulating Argyll-Robertson pupils are common. The following summary illustrates findings which are typical of the mild symmetric neuropathy.

Case 1. A 38 year old man noted burning of the soles of his feet two years before entry. This was worse at night and awakened him four to five hours after retiring. This gradually increased in severity, extending to the dorsum of the feet and to the ankles. For six months he had noted impotence. Diabetes mellitus was discovered two and a half months before admission to this hospital, and he had been placed on a diet and given 20 units of N.P.H. insulin daily. Following

From the department of neurology, neurosurgery and psychiatry (neurology), New England Center Hospital, and the department of medicine, Tufts University School of Medicine, Boston, Massachusetts.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 25, 1957.

TABLE 1

Symmetric Neuropathy—
Onset gradual.
Diabetes of long duration, uncontrolled or severe.
Predominantly sensory.
Symmetric, distal.
Adequate control necessary for improvement.
Asymmetric Neuropathy—
Onset often sudden.
May occur as first indication and in mild or latent diabetes.
Pain, weakness, atrophy prominent.
Characteristically mononeuropathy or radiculopathy, asymmetric, proximal or distal.
Prognosis good—even in uncontrolled diabetes.

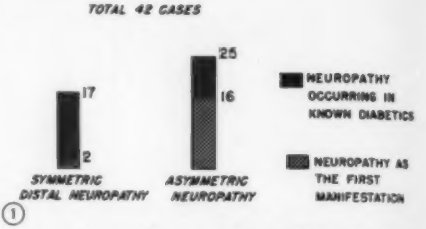


FIG. 1. Asymmetric neuropathy or radiculopathy is a common first manifestation of diabetes mellitus. This is rarely true of the symmetric distal neuropathy of diabetes.

institution of this regime, he noted an increased intensity of the burning and began to note numbness and tingling of the fingers of both hands. Examination revealed a plethoric individual. His mental status was normal. Cranial nerve examination revealed no abnormality, but funduscopic examination showed capillary aneurysms. Strength was normal throughout, but Achilles reflexes were absent. Sensory examination revealed diminished response to pinprick over the sole and dorsum of both feet and at the tips of the fingers. Relevant laboratory findings included only glycosuria, fasting blood sugar of 159 mg. per cent, and spinal fluid protein of 73 mg. per cent.

Comment. Although diabetes had been discovered only two and a half months before admission, the presence of the diabetic microaneurysms in the retina indicated that the patient had had diabetes for a number of years.[1] A second point of interest is that the patient noted increasing intensity and progression of his symptoms following the institution of treatment by diet and insulin. This is a common phenomenon which is not understood.

The next case demonstrates a symmetric distal, predominantly motor neuropathy, which, in our experience, is a much less common variant.

Case 2. A 54 year old restaurateur noted gradually increasing weakness of his legs over a two and a half year period. This resulted in a slapping gait and instability of posture, so that he could not regain his balance if pushed. He noted that his shoes felt loose and strange on his feet, but he did not complain of numbness or paresthesias. He had no pain or cramping of his leg musculature. Bladder sensation and function were normal. Pertinent physical findings were marked atrophy of all musculature below the knees, together with virtual paralysis of dorsal flexion of feet and toes and of inversion and eversion. Extension of his feet was approximately 50 per cent of normal strength. The right patellar reflex and Achilles reflexes were absent and his left patellar reflex was barely elicitable. Sensory examination indicated a diminished sensibility to pain and touch, with a fading upper border at the ankles. Vibration sensibility was diminished at toes and position sensibility was slightly defective. A glucose tolerance test revealed a fasting blood sugar of 121 mg. per cent; one-half hour 228 mg. per cent; one hour 238 mg. per cent; and two and one-half hours 140 mg. per cent.

TABLE 2

	Number of Cases	*Known Diabetes*
Symmetric, distal neuropathy	11	9
Symmetric, distal, plus asymmetric motor neuropathy	6	6
Asymmetric motor neuropathy	25	9
Total	42	24

ASYMMETRIC MOTOR NEUROPATHY

Twenty-five of the 42 cases in this series had a syndrome usually ushered in by pain and associated with the development of weakness and muscle wasting. Sensory impairment was less prominent and was variable in occurrence. The distribution of pain, motor weakness, and sensory loss, if present, suggested that spinal roots or peripheral nerves might be affected singly or in an asymmetric pattern. The majority of these cases (16 of 25) were not known to be diabetic at the time of admission to the hospital, and were found to have fasting blood sugar levels within a normal range (figure 1). The neuropathy was the first evidence of diabetes in many of these patients, and the disease was mild and readily controlled by dietary measures alone.

The following case typified the asymmetric motor neuropathy described in this report.

Case 3. A salesman aged 58 was referred because of low back pain. He had been aware of having diabetes for at least five years, had been

on a diet, and was taking 25 units of insulin per day. His work required that he go to Europe for a few months, during which time he took insulin very irregularly and neglected his diet. He found, thereafter, that he had an increased need for insulin. Upon his return, he noted pain in his back which extended down into the left leg to the calf. It was also present to some extent in the right leg. The pain was a dull, aching discomfort. Rest did not relieve the patient; in fact, he obtained relief by moving about. He had become aware of numbness in the left foot. On examination we found that he was an intelligent, moderately obese person. The pertinent findings on examination were a blood pressure of 160/90 and a liver edge which was smooth and two fingers' breadth below the right costal margin. Examination of his fundi showed scattered hard exudates. The pupils were slightly irregular, reacting poorly to light and better to accommodation. The remainder of the cranial nerves did not reveal any significant abnormalities, nor did his upper extremities. Examination of his back revealed good movement of the lumbar spine. There was no localized tenderness, and straight leg raising was limited on neither side by discomfort. He had marked weakness and atrophy of the left gluteus, the thigh adductors, and the quadriceps muscles on the left. There was weakness of all movements of the left ankle and toes. It was not possible to demonstrate weakness or atrophy on the right side. However, patellar and Achilles reflexes of both legs were absent and plantar reflexes were flexor. Sensory examination revealed that there was a diminution of pain and touch sensibility in stocking distribution to below the knee on the left leg.

The patient was readmitted after two months of careful supervision of diet and insulin requirements. He had also been treated with large doses of vitamin B_{12} and pregnant mammalian liver extract. However, the pain continued as before and now became worse on activity. Weakness increased and the patient was required to use a cane because of the marked weakness of the left leg. He had now lost a total of 20 pounds since the onset of the illness. Examination at this time revealed increased weakness and atrophy of the gluteus, the adductors of the left thigh, the quadriceps, and marked weakness of the iliopsoas muscle. The patient remained unable to rise on the toes of the left foot. Dorsiflexion of the foot and toes seemed stronger. Sensory disturbance in the left foot and leg appeared less marked, and now pain and touch sensibility was questionably diminished on the lateral aspect of the foot and leg below the knee.

At this time the diagnosis of diabetes mellitus was called into question. The fasting blood sugar was 81 mg. per cent. A glucose tolerance test showed a fasting blood sugar of 83 mg. per cent; at one-half hour 195 mg. per cent; one hour 236 mg. per cent, and at two and one-half hours 177 mg. per cent. There was glycosuria from 0.1 gm. to 0.244 gm. in all four specimens. Spinal fluid examination showed two cells and protein of 75 mg. per cent. A myelogram, including cervical, dorsal, and lumbar areas, was entirely normal.

Thereafter, the patient was examined at regular intervals during the next 20 months. Eight months after the onset and six months after the first examination, the patient began to note a lessening of the pain and an improvement in strength. However, he had developed pain in the lateral aspect of the left arm, extending into the ulnar aspect of the forearm, with weakness of hand musculature. Examination revealed a weight gain of ten pounds (from 159 to 169 pounds). He now showed weakness of muscles of the left thenar eminence, although no atrophy was apparent. Examination of the lower extremities showed an improvement in the strength of muscles involved and the right patellar reflex was now present. Sensory examination was negative at this time.

Two months later the patient had gained another ten pounds, reported that he felt quite well, had discarded his cane, and was walking unaided. Examination revealed weakness in the left hand which had remained the same. In the lower extremities there was some weakness and atrophy of the gluteus, quadriceps, and adductors—slight in comparison with that noted previously. The patient was able to rise on the toes of either foot. Examination one year from the date of onset showed only minimal weakness of opponens pollicis of the left hand. There was remarkable improvement in the strength of the leg, with no obvious weakness and no disturbance of gait. The right patellar reflex was now two plus, the left one plus. Achilles reflexes were not elicited. At this visit the patient complained for the first time of cramping pains in both calves on walking.

When last examined, 21 months after the onset of the illness, the patient admitted to neglecting his diet again. There was an increase in the intermittent claudication, so that pain forced him to rest after walking one city block. Sensory examination showed a diminution to pain and touch sensibility extending to the ankles. A two hour postprandial blood sugar was 262 mg. per cent.

Comment. This case was presented in detail to illustrate the cardinal features of a distinctive neurologic syndrome. It is important to realize that this patient did not cooperate sufficiently to maintain satisfactory and sustained control of his diabetes. Yet he recovered completely from the asymmetric motor neuropathy and developed a distal sensory neuropathy. This is consistent with our experience, for it illustrates the tendency toward spontaneous recovery demonstrated by the majority of our patients with asymmetric diabetic neuropathy. It is questionable whether there was a relationship between vascular insuffi-

ciency and the development of the symmetric sensory deficit.

The following two cases demonstrate variants of this syndrome.

Case 4. Weakness without pain or sensory loss. A 59 year old housewife noted weakness of the left foot and ankle about two weeks before admission, and within two days she was totally unable to extend her foot or turn it laterally. There was neither pain nor sensory symptoms. Examination showed that the left pupil was slightly irregular and did not respond to light or accommodation. The optic fundi were normal. There was a foot drop on the left, with virtual paralysis of dorsal flexion of foot and toes and weakness of inversion and eversion of the foot. The patient had a steppage gait on the left. The patellar reflex was diminished on the left and the Achilles reflex diminished on the right. There was no sensory disturbance. A glucose tolerance test showed a fasting blood sugar of 93 mg. per cent; 241 mg. per cent after one-half hour; 249 mg. per cent after one hour; and 177 mg. per cent after two and one-half hours. There was no sugar in the urine at any time. While in the hospital the patient developed a left facial paralysis of peripheral type, which began to improve before discharge from the hospital.

Cranial neuropathy in diabetes mellitus is also characterized by sudden onset, asymmetry, and good prognosis, and thus resembles the asymmetric neuropathy described. The facial paralysis mentioned in case 4 was considered to be related to diabetes.

TABLE 3

RESULTS OF GLUCOSE TOLERANCE TEST IN PATIENTS NOT KNOWN TO BE DIABETIC PRIOR TO DIAGNOSIS OF NEUROPATHY

Case Number	*Fasting*	*One-half Hour*	*One Hour*	*2½ Hours*
1	103	222	276	228
2–	–	166	214	323
3*	103	217	140	131
4	131	234	266	137
5	119	202	297	195
6 June 4	88	195	211	175
June 22	101	177	240	261
7	195	308	405	348
8	93	241	249	177
9	88	173	199	186
10*	107	194	190	108
11	97	164	213	206
12	98	172	202	196
13	150	168	195	152
14	114	186	219	225
15	120	209	300	184
16*	88	195	255	97
17	120	166	195	221
18 April 14	93	191	138	105
May 27	157	173	228	190

*Suspicious, but not diagnostic of diabetes.
Cases 1 and 2: Symmetric distal neuropathy.
Cases 3 through 18: Asymmetric neuropathy.

Case 5. Pain and weakness without sensory change. A housewife aged 71 noted the onset of pain two months before admission. The pain started in the lateral aspect of the right foot, and progressed to the lateral calf and to the posterior aspect of the right thigh. She had no increase of pain on bending, coughing, or straining. Weakness developed within a few days and she was unable to dorsiflex the right foot. There had been no sensory symptoms. She had no polyuria, polydypsia, or other symptoms of diabetes. Six months before admission she had had "shingles" that affected the left side of the forehead and scalp and the left eye. Examination revealed a moderately obese woman, alert and cooperative, with a normal mental status. Funduscopic examination revealed no hemorrhages, exudates, or aneurysms. Positive findings were limited to the right leg, which showed slight weakness of flexors of the thigh, paralysis of dorsal flexion, inversion and eversion of the foot and of the extensors of the toes, including the great toe. There was no pain, percussion tenderness, or limitation of movement of the lumbar spine. A glucose tolerance test revealed a fasting blood sugar of 195 mg. per cent; after one-half hour 308 mg. per cent; at one hour 405 mg. per cent; and at two and one-half hours 348 mg. per cent. At one hour there was 0.9 gm. and at two and one-half hours 6.2 gm. of sugar in urine specimens.

NEUROPATHY IN LATENT DIABETES MELLITUS

Our material leads us to agree with Jackson,[2] who stated, "The cause of diabetes is not known, nor its real relation to growth and

TABLE 4

FASTING BLOOD SUGAR AND GLUCOSE TOLERANCE TEST IN PATIENTS KNOWN TO BE DIABETIC PRIOR TO DIAGNOSIS OF NEUROPATHY

Case	1 (S)*	135
	2 (S)	166
	3 (S)	159
	4 (S)	164
	5 (S)	156
	6 (S)	132 to 173 (6 tests)
	7 (S)	182
	8 (S)	166—214—323
	9 (S)	166
	10 (M)*	257
	11 (M)	175—262—424—294
	12 (M)	163—279—385—394
	13 (M)	129
	14 (M)	120 to 165 (6 tests)
	15 (M)	148
	16 (A)*	168
	17 (A)	73—158—201—131
	18 (A)	83—195—236—177
	19 (A)	195
	20 (A)	143—217—300—296
	21 (A)	177
	22 (A)	154
	23 (A)	199
	24 (A)	160

*(S) Symmetric distal neuropathy.
*(A) Asymmetric neuropathy.
*(M) Mixed.

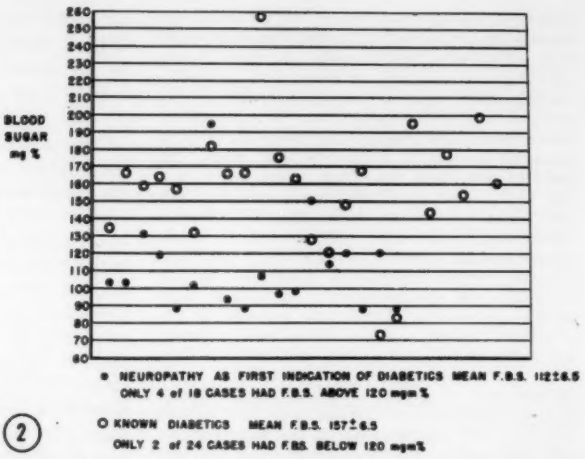


FIG. 2. Fasting blood sugars in known diabetics and in patients presenting with neuropathy as the first indication of diabetes.

size understood, but apparently diabetes in the latent form ("pre-diabetes") remains with the victim years or decades before he or she becomes overtly diabetic." One must be careful, however, to define latent (hidden) diabetes as a clinical state in which there are neither classic symptoms nor signs of diabetes and in which the laboratory examination is inconclusive. In such cases the fasting blood sugar is usually normal, there is no glycosuria, and the glucose tolerance test may be suspicious, either by reason of an excessive rise in blood sugar in the one-half hour or one-hour specimen, or because the two and one-half hour blood sugar is slightly elevated. Table 2 indicated that 15 of the 17 patients entering the hospital with a symmetric distal or mixed neuropathy were known to be diabetic, and only nine of 25 of those with asymmetric motor neuropathy were known to be diabetic. Table 3 lists the results of the glucose tolerance tests in those patients who presented with the neuropathy as the first evidence of diabetes. The majority (15 of 18) had an asymmetric neuropathy, and only four of those 18 cases had an abnormal fasting blood sugar. Case 18 illustrates the fact that some patients with mild diabetes may have a normal glucose tolerance test when first examined, but a repeat examination (under controlled conditions) will reveal the diagnosis. As noted, a single examination in cases 3, 10, and 16 did not establish the diagnosis. However, there is a family history of diabetes in each case, and the patients presented with a neuropathy for which no other cause could be adduced. Table 4 reveals a rather startling contrast. Fifteen of the 24 cases had either a symmetric sensory or mixed neuropathy. Only two of the 24 cases had normal fasting blood sugars (cases 17 and 18) and both were examples of asymmetric neuropathy.

Figure 2 illustrates graphically the contrast between the two tables. This emphasizes facts that have not found general agreement among physicians; namely, that neither a fasting blood sugar test nor an absence of glycosuria rules out diabetes mellitus. We do not consider that all 18 patients who were not known to be diabetic at the time of admission to the hospital were "latent" diabetics, for a glance at table 3 would indicate that a number of them were overtly diabetic. The following case, however, may serve to illustrate the point that symptoms suggestive of damage to the peripheral nervous system may antedate overt diabetes.

Case 6. A 46 year old man was first admitted to the hospital complaining of pain of radicular distribution, radiating from the mid-dorsal region anteriorly into the left abdomen. This was dull and aching in character, constant, and without relation to movement or posture. Neurologic examination was said to be negative. He had no glycosuria and a blood sugar test was not done. Two years later he re-entered the hospital complaining of a recurrence of the pain in the left flank and

abdomen. In addition, during the preceding two months he had noted a burning sensation of his feet which was most marked at night. Again, neurologic examination was reported as negative. Fasting blood sugar on this occasion was 110 mg. per cent, and when repeated was 94 mg. per cent. Seven years after the first admission, he was readmitted because of a recurrence of pain. This radiated now from the upper lumbar region into the right lower quadrant, down into the right testis, and was burning and aching in character. There was a recurrence and increase in severity of the burning of the feet. He also complained of pain over the left scapula, which was burning in quality and was unrelated to movement. Neurologic examination at this time revealed an absence of Achilles reflexes, diminished vibratory sensibility at toes and ankles, and diminished pin and touch sensibility extending onto the dorsa of both feet. A glucose tolerance test revealed a fasting blood sugar of 150 mg. per cent; at one-half hour 168 mg. per cent; at one hour 195 mg. per cent; and at two and a half hours 152 mg. per cent. There was 0.85 gm. of sugar in the urine specimen at two and one-half hours. At no time had roentgenograms of the spine revealed evidence of any abnormality. Examination of the genitourinary system, including a pyelogram, had been entirely negative.

Comment. We believe that this patient's symptoms, dating back several years, were related to the diabetes which was discovered ultimately. It is possible that a glucose tolerance test obtained at an earlier admission, or at least a two-hour postprandial blood sugar after a test meal, might have shown diabetes.

DISCUSSION

Evaluation of our material indicates that diabetic neuropathy assumes one of two forms — 1) an asymmetric, painful, predominantly motor neuropathy, or 2) a symmetric, distal, predominantly sensory neuropathy. It is acknowledged that patients with diabetes mellitus may have pain syndromes in various parts of the body without objective findings, and that other patients are without symptoms and demonstrate absent Achilles reflexes and diminished vibratory sensibility. It seems reasonable, however, that those with pain, but without objective findings, properly belong with the group of asymmetric neuropathies. We suggest that damage to roots or peripheral nerves is less severe or occurs in trunk segments, and thus it may be impossible to demonstrate motor or sensory findings in these cases. The second group seems to be symmetric distal neuropathy, again being milder in degree. Several classifications have been given in the literature, all differing in minor details,[3–5] and it may be that the foregoing is an oversimplification.

Although we are not in a position to judge the relative frequency of the occurrence of the asymmetric neuropathy as it relates to the entire picture of diabetic neuropathy, experience suggests that it is not a rare or unusual complication of diabetes. Bailey[4] urged caution in attributing femoral, sciatic peroneal, and ulnar neuropathy to diabetes and suggested that other causes be sought. Mindful of this, we have taken care to exclude causes such as peroneal pressure and ulnar palsy, herniation of intervertebral disk, herpes zoster, and other possible causes of spinal root or peripheral nerve damage.

Unfortunately, pathologic studies of diabetic neuropathy contribute little information regarding pathogenesis. Nevertheless, clinical experience teaches us that the neuropathy of a metabolic deficiency in general should be a distal symmetric affection, and the author is inclined to believe that the symmetric neuropathy of diabetes may be related to a long continued fault in metabolism. Our material tends to support this, for 15 of 17 patients were known to be diabetic for an average duration of six years before entry, with the duration of known diabetes ranging from two and one-half months to 20 years. The presence of a diabetic retinopathy in a majority of these patients indicates diabetes of several years' duration, despite the fact that it may have been discovered only within recent months, for example, case 1. However, the totally dissimilar asymmetric neuropathy, as herein described, might well have a different etiology. Clinically, it closely resembles the neuropathy of periarteritis nodosa which has been shown to be caused by involvement of the nutrient vessels of the peripheral nerve.[6,7] However, there appears to be an unwillingness to accept a vascular origin for this type of neuropathy in diabetes.[8] The point has been made that some of these patients have shown no clear evidence of arteriosclerosis, and thus it would seem unlikely that vascular change in peripheral nerves should be considered.[9,10] Conversely, one might point out that nondiabetics

with severe arteriosclerosis do not develop an asymmetric motor neuropathy. The good prognosis in this type of diabetic neuropathy has been used as evidence against vascular etiology.[10] We believe that occlusion of a nutrient vessel need not seriously impair the blood supply to a nerve, but may cause transient and relative ischemia sufficient to produce the changes described, and yet be consistent with repair and recovery.

The possibility that there is a specific vascular disease in diabetes has been raised by Lundbaek.[1] He presented evidence that favors the hypothesis of a specific diabetic angiopathy, which is not identical with arteriosclerosis or other more or less well-defined vascular diseases. The congested, beaded retinal veins, the typical retinal microaneurysms, and the hyalin masses between capillary loops in the kidney glomeruli are pathognomonic of diabetes. Is it not reasonable to suggest that the vasa nervorum may also be the site of vascular disease in diabetes?

Fagerberg[11] reported finding a constriction of the lumina and thickened walls of the vasa nervorum in diabetic neuropathy. Staining characteristics suggest that this occurs as a result of deposition of mucopolysaccharides. Further pathologic studies may substantiate this finding. The clinical features in the asymmetric neuropathy of diabetes appear to be consistent with a vascular etiology. Perhaps our difficulty in understanding the pathology of diabetic neuropathy has been due to an assumption that diabetic vascular disease is identical with nondiabetic arteriosclerosis, and also due to a failure to make a distinction between two dissimilar syndromes which, from a clinical viewpoint, could have different pathogenesis.

SUMMARY

Diabetic neuropathy assumes two distinct forms: one, a symmetric distal neuropathy; the other, an asymmetric, predominantly motor neuropathy. Whereas the former occurs in diabetes which is inadequately controlled or of long duration, the latter is often the first evidence of mild diabetes and tends toward spontaneous recovery.

The contrasting clinical syndromes are described and the conclusion is drawn that such contrast suggests a different pathogenesis.

REFERENCES

1. Lundbaek, Knud: Diabetic angiopathy. A specific vascular disease. Lancet 1:377, 1954.
2. Jackson, W. P. U.: A concept of diabetes. Lancet 2:625, 1955.
3. Treusch, J. V.: Diabetic neuritis. A tentative working classification. Proc. Staff Meet., Mayo Clin. 20: 393, 1945.
4. Bailey, A. A.: Neurologic complications associated with diabetes. Diabetes 4:32, 1955.
5. Goodman, J. J., et al.: Diabetic Neuropathies. Am. Lecture Series, No. 151. A monograph in the Bannerstone division of lectures in endocrinology. Springfield, Illinois, Charles C Thomas, 1953.
6. Wohlwill, Friedrich: Ueber die nur mikroskopisch erkennbare Form der periarteriitis nodosa. Arch. path. Anat. 246:377, 1923.
7. Kazmeir, F.: Der vasale Faktor bei Erkrankungen der peripheren Nerven. Nervenarzt 21:353, 1950.
8. Garland, Hugh: Diabetic amyotrophy. Brit. M. J. 2:1287, 1955.
9. Goodman, J. J.: Etiology of the diabetic neuropathies. Am. J. Digest. Dis. 22:236, 1955.
10. Martin, M. Mencer: Diabetic neuropathy, a clinical study of 130 cases. Brain 76:594, 1953.
11. Fagerberg, Sven-Erik: Studies on the pathogenesis of diabetic neuropathy. Survey of the literature and own working hypothesis. Acta med. scandinav. 154: 145, 1956.

Uncinate fits

David Daly, M.D.

In 1899 Hughlings Jackson[1] wrote: "I have several times drawn attention to what I will now call a group of cases of epilepsy – cases in which there is at the onset of the paroxysms a crude sensation of smell or of taste or in which there are movements of chewing, smacking of the lips, and sometimes spitting, etc."

For these seizures, Jackson proposed the name "uncinate group of fits," basing this term on the observations of Ferrier, who had concluded from animal studies that smell and taste are localized in the uncinate gyrus. Although Jackson created a formal category of seizures whose name, "uncinate fits," has remained to this day, olfactory and gustatory hallucinations had been recognized as manifestations of epileptic discharge at least 30 years earlier.

There is little purpose in attempting to assign priorities for the first description of olfactory or gustatory hallucinations; however, it may be mentioned that in 1867 Herpin (cited in Jackson and Stewart[2]) reported on three patients who experienced "fausses perceptions d'odeurs" at onset of the attacks. In 1874 Sander[3] described a patient whose attacks were preceded by "a dreadful, disagreeable smell," followed by masticatory movements and salivation. At necropsy a large tumor was found in the frontotemporal region. At about the same time Falret, in an undated reference, was quoted by Jackson[4] as describing olfactory auras to attacks. In 1875 Jackson[5] commented on the condition of two patients; one was subject to attacks "beginning by a 'subjective' sensation of smell," and the other at the onset of her seizures said: "What a dreadful stink there is in the place!"

The concept of uncinate fits gained ready acceptance, and there were numerous contemporary references to seizures with olfactory and gustatory hallucinations. However, in succeeding years there has been a declining interest in these phenomena. In recent years papers dealing with the problem have been rare. Somehow the masticatory and salivatory components of the attacks have been elided and nowadays the term is limited to olfactory and gustatory hallucinations.

The exact incidence of these seizures is difficult to estimate. Gastaut and associates,[6] on the basis of 1,000 patients, have reported an incidence of 5.9 per cent, while Lennox and Cobb[7] observed only 2 per cent. Such figures are valuable in indicating the order of magnitude of the condition, and it is certainly true that such seizures are relatively rare.

MATERIALS

Observations on 55 patients form the basis of this report. The patients were seen by my colleagues or myself over a period of several years. Twenty of the patients had tumors which involved the temporal lobe. Eleven of these lesions proved to be astrocytomas, four oligodendrogliomas, and one an epidermoid. In four instances, although radiographic contrast studies demonstrated tumors, histologic verification was not obtained. One patient had an aneurysm of the internal carotid artery in the region of the sella turcica and one patient had tuberous sclerosis. In six patients pneumoencephalography gave evidence of focal atrophy. In some instances this was consequent to trauma or vascular occlusions. Fourteen other patients exhibited electroencephalographic evidence of abnormal discharges occurring in the temporal region. In ten patients these consisted of foci of spike discharges, and in four there were random, irregular, slow waves arising from the temporal area. In the remaining patients there were no clues as to the nature of the pathologic process.

OLFACTORY PHENOMENA

A wide variety of olfactory experiences occurs; some are surprisingly complex. In general, they may be divided into hallucinations and illusions. The hallucinations in turn range

From the section of neurology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Read at the meeting of the American Neurological Association, Atlantic City, New Jersey, June 17 to 19, 1957.

from crude olfactory sensations to elaborate hallucinations which may include visual or auditory components.

Hallucinations. The olfactory hallucination most frequently described was a crude, undifferentiated sense of smell without gustatory components. This was reported by 20 patients. The patients employed a variety of terms in attempting to characterize these odors. Usually, the terms were comparative, and the patients said that the smell was "like lacquer," "like coal-gas," or "like the smell of a skunk." Gastaut and his associates[6] have attempted to classify these odors into five major groups; however, as they recognized, this is of dubious value since often it reflects only the past experiences of the patient. Thus, one of their patients at first said he smelled chloroform but later decided it was ethyl chloride. When given an opportunity to smell both gases, he said the hallucination was not like either of them!

After careful questioning and an attempt at precise description, patients usually concede that the odor is not any recognizable smell and that actually it is indescribable. Many patients recognize this initially and say that the odor is not familiar to them. Nevertheless, the character of the hallucination seems unchanging, so that patients recognize it as the same in each attack. It is not surprising that most olfactory hallucinations are indescribable. Attacks arising in the primary receptive areas for other sensory modalities similarly produce crude and undifferentiated sensations; for example, a patient may describe somatosensory seizures in such terms as "numbness," "tingling," or "prickling," but never as a well developed tactile perception. Thus, most olfactory hallucinations are analogous to those involving other sensory modalities.

The majority of patients attribute some affective quality to the olfactory hallucinations and refer to these experiences as pleasant or unpleasant. With hallucinations in other sensory modalities, such affective connotations are uncommon. Eight patients reported the olfactory hallucinations as unpleasant. They spoke of them as "very disagreeable," "a horrible smell," "nauseating," or "a terrible rotten odor." Interestingly enough, however, four patients described the hallucinations as pleasant. One patient said: "It's pleasant, but I can't recall it afterward." Another patient said the odor was pleasing and somewhat like the smell of frying meat. Although most authors emphasize the disagreeable quality of the odors, some have noted that this is not invariably so. Mills[8] reported upon a patient who described the smell as unrecognizable, but something like that of a flower. Even more fortunate was the patient of Wilson,[9] who said of her hallucination that it was "like passing a perfume shop." Nine patients felt that the olfactory experiences were neither pleasant nor unpleasant but, rather, had a "neutral" character.

Generally the olfactory hallucinations are not lateralized, nor does the patient have the impression that the smells are arising externally from the environment. However, one patient reported that the smell seemed to be in one nostril.

ILLUSTRATIVE CASES

Case 1. A 48 year old man was found to have an astrocytoma, grade 4, involving the left temporal lobe. In the six weeks prior to examination he had experienced up to six minor seizures daily. Initially, the attacks had consisted of a sudden, indescribable but unpleasant odor which seemed to be in the left nostril, followed by a sense of confusion and faintness. The patient recognized the odor as a hallucination. Later, the attacks were longer and the patient had difficulty in finding words during them. At this time he felt "dreamy."

Examination revealed some impairment in the perception of wintergreen and camphor if the odor of these was inhaled through the left nostril. Examination of the visual fields revealed congruous upper quadrantic defects in the right homonymous fields. There was mild aphasia.

One of the examiners witnessed an attack. The patient said: "Here is one now. I smell that odor again, more on the left side. Now my head feels funny, hard to think or talk." He made swallowing movements; his speech became thick and he groped for words. The seizure lasted about two minutes, after which he was confused.

Rarely, patients have what may be termed "formed" olfactory hallucinations. In such instances the patients describe the odor as recognizable.

Case 2. A 41 year old woman was seen because of seizures of seven years' duration. These had begun two months after severe pre-eclampsia, with hypertension and edema, which resulted in a stillbirth.

The attacks were preceded by the sensing of a vivid odor of peaches, followed by a feeling that "I'm not really myself." Frequently there was a sense of familiarity. She would feel generally weak and her heart would pound. She might remain dazed for a few minutes, but more often she would fall unconscious. Several times she had injured herself by falling over the stove or striking her head. Occasionally the odor of peaches would recur after the seizure. The hallucination was so vivid that originally she was certain that there must be peaches in the room. She would inquire of her family or friends if they could smell the peaches. In time, puzzlement changed to suspicion and the patient concluded she must be hallucinating. She ceased mentioning these experiences, but the hallucination of peaches always remained so intense that it seemed real to her.

Neurologic examination showed no abnormalities. An electroencephalogram revealed slow, 4-cycle-per-second rhythms from both temporal regions. Results of pneumoencephalograms and carotid angiograms were normal.

Even more unusual are certain cases in which the olfactory sensations are but part of an elaborate hallucination. None of my patients reported such experiences, but Gowers[10] has described one patient with an intricate aura which included the visual hallucination of an old woman wearing a brown dress who appeared to offer the patient something that smelled of "tonquin beans." Foster Kennedy[11] saw a patient with a tumor of the temporal lobe who experienced attacks in which "she suddenly heard a bell ringing, then saw a 'strange, bad woman' clad in rags, and smelled a most evil odor which originated, she [the patient] thought, in the stranger's clothes."

Jackson and Beevor[12] described a somewhat different situation. Their patient would see "a little black woman who was always rather agreeable." This little woman seemed to be actively engaged in cooking, and was "always flitting about the kitchen." At the same time the patient would note an unpleasant odor which she described as "burning, dirty stuff." In this instance, the olfactory hallucination apparently was not related to the visual hallucination, although the latter involved the kitchen and cooking.

In some instances olfactory hallucinations involve a sense of familiarity and may evoke old memories. Gastaut and associates[6] referred to one patient in whom an odor of resin was accompanied by a vision of a field bordered by pines. Such an experience may be termed an "olfactory reminiscence."

One patient in this series described a similar situation.

Case 3. A 26 year old man had had infrequent, generalized convulsions since infancy and minor attacks since the age of three years. In recent years minor attacks had occurred on the average of twice weekly. For several hours before the attack he would note an indescribable but unpleasant taste. This was associated with anorexia, although food had a normal taste. A smell signaled the onset of a seizure. The smell was not always the same; in fact, he believed there were two or three different odors. At the time of the attack each was familiar, but after the attack he could not recollect exactly what it had been. However, the hallucinations always seemed to recall odors of cooking in his mother's kitchen when he was a child. The smell was followed by a feeling of intense fear and a conviction that someone was standing behind him. He would perspire profusely and his mother observed that this was followed by staring, flushing, masticatory movements, and confused automatic behavior.

Electroencephalography revealed sharp-wave discharges in the right temporal region. Pneumoencephalograms and angiograms disclosed nothing abnormal.

Although this patient could not remember their exact nature, the hallucinations seemed to evoke early olfactory memories. Penfield and Jasper[13] have described analogous examples of memories called forth by ictal discharge.

In summary, a crude and unrecognizable smell is the most common olfactory hallucination. Often the odor is neutral, although it may be either pleasant or unpleasant. Occasionally the odor may be recognizable. It also may be a part of a complex multisensorial hallucination. Rarely, the hallucination may have a familiar quality, suggesting a reminiscence or memory.

ILLUSIONS

In the presence of olfactory illusions, an alteration in the character of normal olfactory stimuli occurs during the seizure. This seemingly is a rare phenomenon, although perhaps more careful inquiry would reveal other examples of it. Cushing[14] remarked upon a patient with a glioma of the left temporal lobe, noting "the attacks are usually accompanied by what he describes as an exaggeration of his special sense impressions, i.e., flowers become extraordinarily beautiful, odors are intensified, his vision appears to be remarkably keen, so that

objects seem to be increased in size." Gastaut and associates[6] described a patient who would notice a sudden change in the smell of cigarette smoke. The odor of the smoke would become intensified and pungent, much like smoke which penetrates railway cars when a train passes through a tunnel. This illusion was accompanied by a prickling in the throat which made the patient cough.

One of the author's patients reported that illusions occurred initially and that classical olfactory hallucinations were noted later. The patient insisted that the illusions were produced by a sudden odor, suggesting an olfactory precipitation of seizures.

Case 4. A 49 year old woman was seen because of seizures that had appeared during the preceding four months. She felt that the first four attacks had resulted from a sudden odor. In her first attack she was preparing a salad when she suddenly noted an intensification of the smell as she poured on salad oil. She felt that she must remember something but could not recall what it was. This was succeeded by nausea, a sense of abdominal distention, and belching. She went to the bathroom because she feared she would vomit. The symptoms disappeared and a few minutes later she returned to the kitchen, where she fell unconscious and had a generalized convulsion. Another attack occurred when a bowl of chili was placed in front of her; again there was a sudden intensification of the odor. Loss of consciousness did not occur. A few days later a third attack took place when she picked up a dish of chicken and noodles. In this attack there were nausea, belching, and borborygmi, with the feeling that she must again recall some event. The fourth attack developed when she lifted the lid off a pot of roasting beef. These attacks were succeeded by others in which there was a sudden odor resembling burnt coffee, followed by nausea, abdominal distention, and belching.

An electroencephalogram revealed a focus of random slow waves from the right temporal region. Pneumoencephalography revealed displacement of the right lateral and third ventricles to the left, suggesting a deep-seated tumor in the right temporal region. The patient declined operation and was treated with deep roentgen therapy. In a letter from her referring physician, it was indicated that subsequently left hemiplegia developed and that the patient ultimately died. Necropsy was not performed.

Perceptual illusions represent a distortion or perversion of sensory stimuli, resulting in subjective awareness of a change in normal perceptions. Perceptual illusions may involve external sensory stimuli or may result in distortions of the body image. Visual illusions, in which objects may seem to become larger or smaller, and auditory illusions, in which sounds become louder or fainter, are most frequently mentioned. Three patients reported illusions coincident with olfactory or gustatory hallucinations, but no patient described illusions involving simultaneous olfactory and visual components.

One man, who had a hallucination of smell and taste "like burning fat," described at the same time a feeling of remoteness and unreality. The room might look too large or too small and his teeth felt "too large, like marbles." Another patient, who had an indescribable, unpleasant olfactory hallucination, noted micropsia and a sense of sounds becoming faint. A woman experienced an unrecognizable gustatory hallucination associated with a feeling of unreality. Objects appeared smaller than normal and sounds took on an echoing quality. Thus, hallucinatory and illusionary phenomena may occur either simultaneously or sequentially in the same attack. Olfactory illusions, although rare, are not essentially different from illusions in other sensory modalities.

Jackson's postulate that the uncus is the cortical center for smell was based on observations in animals by Ferrier. Subsequently, reports of findings at necropsy have supported this view. Tumors are of lesser value because of the imprecision introduced by their size and the distortion of surrounding tissues. Jackson and Beevor[12] described a tumor invading the anterior portion of the temporal lobe, including the amygdaloid nucleus, but sparing the "uncinate convolution." Buzzard's[15] patient, who had sustained gustatory disturbances but apparently no true gustatory fits, had a glioma which involved the hippocampal gyrus and destroyed the uncus. Mills'[8] patient, who experienced olfactory hallucinations, was found to have a glioma infiltrating the hippocampus. Atrophic lesions are found less frequently, but are more informative because of their demarcation from normal brain. Hamilton[16] described a case in which a woman suffered from disagreeable olfactory hallucinations "sometimes of smoke, sometimes of a foetid character." At necropsy there was an atrophic area with pial adhesions involving the inferomesial portion of the anterior half of the temporal lobe. Worcester[17] reported a man with olfac-

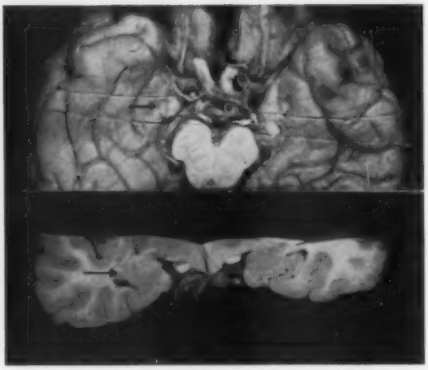


FIG. 1. *A.* Base of the brain of the patient in case 5. Arrow points to gliotic nodule in the right uncus. *B.* Coronal section of the brain, same patient. Arrow points to region of the right uncus. Note loss of normal architecture of the cortex. A description of the findings at microscopic examination is to be found in the text.

tory hallucinations in whom necropsy disclosed an area of softening in the left uncus. On the contrary, Jackson and Colman[18] described a cystic softening of the left uncus in a physician subject to masticatory seizures entirely without olfactory or gustatory components; however, Jackson interpreted the "tasting movements" as indicating "discharge of gustatory elements of the cortex."

In this series three patients came to necropsy. Two patients had gliomas invading the temporal lobe. Both lesions involved the temporal lobe so extensively as to contribute little to the precise location of the olfactory centers. One patient had a small atrophic lesion.

Case 5. In 1949 a 60 year old man was first seen because of seizures that had been present since the age of 14 years. The attacks began with an indescribable feeling in the nose and head, followed by an unrecognizable, unpleasant "nauseating" odor. The odor was so intense that he would go outside or open the windows in the hope that fresh air would stop the attack. He felt weak in the knees and feared he would lose consciousness, although only rarely did he become unconscious. His wife observed that his face flushed at first and then blanched profoundly. These minor attacks occurred at irregular intervals several times yearly. They became less frequent after the age of 25 years and since then he had not lost consciousness. He sought medical advice in 1949 because of a sudden attack of unconsciousness of indefinite duration, followed by confusion and disorientation that had persisted for two days. After this, there was an increase in the frequency of seizures, and the patient complained of difficulty with his memory. He was given anticonvulsant drugs, which brought about some reduction in the frequency of seizures. On one occasion he failed to take his medicine for some time and experienced several generalized convulsions. At the time of his last examination in 1952 he was hospitalized for studies; a cerebral hemorrhage developed and he died.

Necropsy was performed by Dr. George P. Sayre, with the following report of findings.

When the calvarium was removed, the brain was seen to be swollen and tight. This was most marked in the left parietotemporooccipital area. An area of softening was palpated, centering on the left fusiform gyrus. When the base of the brain was examined, the right temporal pole was seen to be blunted, somewhat enlarged, and firm on palpation.

Horizontal sectioning of the brain revealed a cavity filled with freshly clotted blood in the left parietotemporooccipital area, laterad to the ventricles, approximately 6 cm. in diameter. It lay closest to the cortex in the inferior temporal area, where partial rupture through the cortex occurred during removal of the brain.

Frontal sectioning through the temporal poles disclosed the right temporal pole to be partially replaced by a firm, whitish mass 2 by 2 by 2 cm., involving the uncus and the amygdaloid nucleus (figure 1). The left temporal pole appeared to be normal. The remainder of the brain appeared grossly normal, the blood vessels showing mild arteriosclerosis.

Histologic examination of the right temporal pole showed marked distortion of the normal architecture. There were numerous scattered areas of focal gliosis and loss of normal cellular pattern. The gliosis consisted of swollen astrocytes, fibrous in character, with associated loss of myelin. Gitter cells were not in evidence. The blood vessels, particularly the capillaries, were prominent and gliosis was most marked in these areas. There was a tremendous number of corpora amylacea in these areas, as well as in the subpial area. More posteriorly, the normal hippocampal gyrus was distorted. This consisted primarily of a loss of substance in the white matter of the dentate gyrus, with replacement gliosis. There were occasional extensions of the loss to involve the cells of the gray matter of the hippocampus, but the granular stratum remained intact. There was no obvious distortion of the blood vessels of the meninges or choroid in the sections of these areas.

The final diagnosis was old gliosis of the right uncus, cause undetermined; recent hemorrhage in the left temporooccipitoparietal areas; and bronchopneumonia.

GUSTATORY PHENOMENA

Although many authors have devoted considerable attention to the olfactory components of uncinate seizures, the gustatory com-

ponents have received less consideration. Most authors agree that gustatory hallucinations are crude and usually unpleasant. Gowers[19] described a hallucination of taste "between sour and bitter . . . . referred to the back of the tongue." Shenkin and Lewey[20] described a patient with a vascular anomaly located in the sylvian fissure. This patient had attacks with "a sour, bitter taste, seemingly coming from his stomach, followed by nausea." Kennedy[11] mentioned a patient who spoke of a taste like "ink." Gastaut and associates[6] wrote that acid and bitter tastes are most common, but also referred to certain indefinable tastes described as "metallic." The identical word has been used by Jackson[21] and Clarke.[22] Recognizable gustatory hallucinations are extremely rare. Spiller[23] discussed the condition of a woman who experienced perceptual illusions and "the taste of raw, unsalted beef in her mouth."

In this series 16 patients reported gustatory hallucinations without olfactory accompaniments. Seven patients described the taste as unpleasant but unrecognizable. One patient said the taste was "neutral." Sour or acid tastes were reported by three patients and bitter tastes by three. One patient spontaneously referred to the taste as "metallic." A salty sensation was reported in one instance.

There were no examples of gustatory illusions as a part of the attack. The reason for this is not clear, although it may be pointed out that patients only occasionally experience attacks while eating, so that such illusions may readily pass unnoticed. Later, we shall see that interictal or postictal gustatory illusions are more common.

In the majority of patients the gustatory hallucination is not lateralized; however, one patient spoke of an abnormal taste on the side opposite to the lesion.

A CASE ILLUSTRATIVE OF GUSTATORY PHENOMENA

Case 6. A 50 year old man described attacks which began with a "dirty bad taste" localized to the left upper gum. He felt that the taste occurred between two teeth. When he experienced this abnormal taste he also had a dreamy, unreal feeling and dimness of vision. Members of his family observed pallor, pupillary dilatation, and confusion. Surgical exploration revealed an oligodendroglioma in the right frontal and temporal lobes.

Eleven patients reported both olfactory and gustatory hallucinations. In three instances one type of hallucination ultimately was replaced by the other. This sequential alteration appeared to represent a progression of the intracranial lesion. Four patients reported the same smell and taste occurring simultaneously. Since many patients fail to recognize that odor is a major component of flavor, it is possible that these were instances of simple olfactory hallucinations. In one patient olfactory hallucinations occurred in the majority of attacks, but occasionally gustatory hallucinations might be present; in another patient the converse was true. Both patients had tumors which were not verified histologically. In only two patients were there consistently simultaneous olfactory and gustatory hallucinations. One patient with a tumor (astrocytoma, grade 3) of the temporal lobe noted a sharp odor like that of lacquer, a bitter taste, and burning in the mouth and throat. The other patient, who had a similar tumor, reported a pungent odor and a sweet taste. Thus, simultaneous hallucinations of taste and smell are uncommon, suggesting that there are separate cortical centers for taste and smell.

The site of localization of taste in the cerebral cortex originally was assumed to be in proximity to the uncus, but in recent years doubt has arisen. Börnstein[24] postulated that taste is localized in the parietal operculum. On the basis of operative findings and electrical stimulation of the cortex, Penfield and Jasper[13] have concluded that taste is localized within the sylvian fissure, probably in the circuminsular cortex superior to the circular sulcus. In this series no patients with gustatory phenomena came to necropsy.

RHINOSTOMAL SENSATIONS

In some patients olfactory or gustatory phenomena are associated with an unpleasant sensation in the nose, mouth, or throat. Occasionally the sensation may occur alone as a part of an attack that is otherwise indistinguishable from an "uncinate seizure." Gowers[19] has referred to these as "nasal warnings" and commented that they usually consist of a sudden tingling in the nose. Twelve of the author's patients commented on such sensations. In seven, these sensations occurred with olfactory or gustatory hallucinations; five pa-

tients reported these in the absence of any hallucinations. Two brief reports of cases will suffice for illustration.

TWO CASES ILLUSTRATIVE OF RHINOSTOMAL SENSATIONS

Case 7. A 45 year old man was struck on the forehead with a hatchet at the age of 11 years. He was unconscious for eight days; when he recovered consciousness he was found to have left homonymous hemianopsia. Minor seizures developed at the age of 41 years. His attacks began with a sensation in the head and a "tingling in the nose, like powerful acid fumes;" there was no odor whatever. He was observed to stare, make chewing movements, and talk incoherently or occasionally repeat a little verse. His wife said the end of an attack was invariably heralded by coughing. Neurologic examination revealed left homonymous hemianopsia. An electroencephalogram demonstrated a focus of random slow waves in the right temporal region.

Case 8. An 18 year old girl had been subject to seizures for two years. The attacks began in the nose with a burning or tingling which descended into the throat and epigastrium. Associated with this was a sensation of fear. She would hear a voice which she thought was her father speaking to her and thoughts would seem to rush through her mind. Her father observed masticatory movements and typical automatisms. An electroencephalogram showed a focus of slow spike discharges in the left temporal region.

These rhinostomal sensations usually are described as an unpleasant burning, tingling, or crawling. Patients have compared them to the sensation produced by the sudden inhalation of strong acid fumes or the unpleasant experience of regurgitation of a carbonated beverage into the nose. The precise significance of these sensations is not clear; however, the fact that they occur coincident with olfactory or gustatory hallucinations suggests that they are not simple oral somatic sensations.

INTERICTAL OLFACTORY AND GUSTATORY DISTURBANCES

In addition to the olfactory and gustatory phenomena which occur during the attack, some patients note disturbances in the intervals between attacks. These may be divided into negative phenomena, consisting of defects in taste or smell, and positive phenomena, consisting of relatively long-sustained hallucinations or illusions. Paralysis of function of the cortical area in which the attack arose is relatively common after a focal seizure. Paralysis of motor function is so well known that it has received the eponymic name of "Todd's paralysis;" however, examples of postictal aphasia or hemianopsia also are relatively common. Postictal anosmia and ageusia are rare; possibly this rarity is a consequence of infrequent testing of olfactory and gustatory sensation. An instance of postictal anosmia lasting 30 to 60 minutes was mentioned by Bennett.[25]

Sustained defects in olfactory or gustatory function have been noted more frequently. A patient of Anderson[26] was found to have a large, solid tumor arising in the region of the pituitary body and compressing the left temporal lobe. The patient had olfactory hallucinations, and on examination was found to have a defective sense of smell in the right nostril. Anderson did not disclose whether or not the olfactory nerve was compressed. Gowers[10] reported a patient with gustatory and olfactory hallucinations caused by a glioma of the right temporal lobe; there was impairment of smell on the right side. Frazier and Rowe[27] examined 48 patients who had verified tumors of the temporal lobe. Six patients had partial or complete anosmia. In three patients the anosmia was on the same side as that of the tumor, in one the anosmia was on the opposite side, and in two it was bilateral. Frazier and Rowe also observed diminution or absence of gustatory sensation in four patients, but did not further discuss the nature of the defect. The patient of Shenkin and Lewey[29] had lost the perception of sweetness on the entire left side of the tongue; this was the side opposite that of the lesion. On the other hand, Spillane[28] felt that even quantitative olfactometry is of little value in localizing intracerebral tumors. The patient in case 1 of this series had an impairment of smell on the same side as that of his tumor. Two other patients also had anosmia. In one it was on the same side as that of the tumor. In the other patient the side on which the lesion was located was unknown. The patients in this series did not undergo quantitative tests of olfactory function, so that these observations are inconclusive.

Some patients remark upon long-sustained disturbances of smell or taste. Occasionally such disturbances may occur entirely without relationship to the attacks. Gastaut and asso-

ciates[6] have reviewed this problem in detail. They observed that olfactory and gustatory illusions of long duration are more common than hallucinations. The condition in case 4 is an example of sustained gustatory hallucination as a prodrome to the seizures. In the author's series another patient who experienced attacks beginning with an unpleasant but unrecognizable taste noted that this might persist throughout the day after an attack. Occasionally hallucinations of unpleasant taste might persist for periods of two days without the development of a seizure. Gastaut and associates[6] have commented that perversions of taste or smell also may occur in patients who have no ictal olfactory or gustatory hallucinations. One patient in the author's series experienced attacks without aura in which she would stare and make swallowing movements and grunting noises. After the seizures there was transient aphasia. Electroencephalography revealed a focus of spike discharges in the left temporal region. The patient commented that nothing tasted normal to her for 24 hours after the attacks.

ASSOCIATED ICTAL EVENTS

Certain events have occurred in association with olfactory and gustatory phenomena with sufficient frequency to attract attention. As was previously mentioned, Jackson and Stewart[2] described movements of licking, chewing, and tasting which they thought signified epileptic discharge of cortical gustatory elements. Subsequent evidence has suggested that masticatory seizures have only a very indirect relationship to uncinate attacks. In the opinion of Magnus, Penfield, and Jasper,[29] masticatory seizures involve a disturbance of consciousness and constitute a type of automatism. Salivation, contralateral facial movements, taste, and smell may be ictal accompaniments, suggesting that the area from which masticatory seizures originate is a sensorimotor region for oral functions. They concluded that, to obtain mastication from the temporal region, a subcortical mechanism must be activated and the most likely subcortical structure is the amygdaloid nucleus. However, in the auras of their 34 patients who experienced masticatory seizures there were only three instances of smell and one of taste.

Conversely, in the author's series of olfactory and gustatory seizures only eight instances of masticatory movements were observed, although in 27 patients there were alterations of consciousness ranging from mental clouding to confused and automatic behavior. In four patients profuse salivation occurred in the absence of any masticatory movements. These findings support the concepts of Penfield concerning masticatory seizures.

Jackson and Stewart[2] also remarked on the association of "dreamy states" or "voluminous mental states," although, as Jackson and Stewart[2,30] were well aware, either might occur without the other. Thirteen patients of the present series described such experiences. Six patients reported a sense of déjà vu. Some described it as a sense of recollection: a feeling that the patient had been in the same place or circumstance before. In others it was described by what Gowers[10] has termed "precurrence;" for example, the patient felt that he could anticipate what would be said next or what action would occur next. Seven other patients experienced complex conceptual illusions in which things seemed strange, unreal, or unfamiliar. Two patients spoke of feeling "not myself," while other patients felt that their usual environment was strange or unfamiliar. Two patients described perceptual illusions relating to their own body image. One had a feeling of unreality and a sense of detachment. The room appeared too large or too small and his teeth felt too large. Another patient noted that his right arm and leg felt as if they were in the "wrong place," by which he meant that they seemed to be at a distance from his body.

Jackson and Stewart[2] commented on the association of ictal affective states with uncinate paroxysms. They noted that in most instances the emotion was unpleasant, but that this was not necessarily so. Weil[31] has suggested a more specific relationship, feeling that olfactory hallucinations most frequently are associated with depression. In the author's series 12 patients reported ictal affective disturbances. Eight patients described sensations of fear or anxiety. One patient spoke of sadness and three reported pleasurable emotions. In four patients the sense of fear was associated with olfactory hallucinations and in four

it was associated with gustatory hallucinations. The feeling of sadness in one patient was associated with an unpleasant odor. Of the three patients who mentioned pleasurable emotions, one said he noted "a pleasant odor" and a "pleasant feeling." The second patient described a pleasant but unfamiliar odor associated with a "quiet" relaxed feeling. In the third patient there was a sense of euphoria associated with an unpleasant "rotten taste." The euphoria was transient and was followed by a feeling of depression. The relationship of ictal affective states to uncinate seizures is again only a very loose one. In a study of 52 patients in whom affect was a stereotyped part of the seizure pattern, the author[32] found only 14 instances of olfactory and gustatory components of the attacks.

Vegetative disturbances were relatively frequent. Thirty-three patients reported 52 types of vegetative or autonomic phenomena. These related to the abdominal viscera in 20 instances. Nine patients had nausea, while seven patients observed visceromotor activity, including belching, borborygmi, or vomiting. Four patients described epigastric sensations. There were 18 instances of disturbances of the vasomotor system, including pallor in ten, flushing in five, and tachycardia in three. Involuntary hyperventilation occurred in four patients. Six patients perspired profusely. My colleagues and I[33] have discussed the significance of such vegetative phenomena as manifestations of epileptic discharge. Our findings suggested that autonomic events are most frequent in association with epileptic discharge in the orbitofrontal, insular, and anterotemporal regions. Thirst is a visceral sensation which is not readily classified and is only rarely reported as a manifestation of epileptic discharge. One patient in the present group described thirst. His attacks began with nausea, followed by a pungent but indescribable odor. He would feel thirsty and usually drank a glass of water at such a time. After this he would be somewhat dazed. Two instances of thirst as an ictal event have been reported by Penfield and Jasper;[13] in both patients the epileptic discharges appeared to arise in the temporal region. No patient in this series reported hunger. Nevertheless, hunger, too, may be part of an aura in rare instances. The author has observed one patient who experienced marked hunger prior to her attacks. Electroencephalography revealed sharp wave discharges from the right temporal region during a seizure.

The phenomena just described regularly constitute the accompaniments of olfactory and gustatory seizures. Other manifestations of discharge in the temporal lobe, such as visual or auditory hallucinations, may occur but they are relatively infrequent.

COMMENT

As we have seen, Jackson's concepts concerning uncinate fits were based on certain clinical observations, plus the experimental findings of Ferrier suggesting that smell and taste are localized in the uncus. However, Jackson advanced no direct evidence that the cortical centers for smell and taste are adjoining. Furthermore, theoretic considerations offer no reason which would establish such proximity. Smell may be thought of as a teloreceptive sense like vision, whereas taste may be regarded as a visceral sensation. Therefore, in some species, there is no more reason to expect an intimate anatomic relationship between the centers for smell and taste than to expect one between those for vision and taste. The present evidence suggests that smell and taste are discrete sensations which possess separate cortical centers. The area for projection of olfactory perceptions appears to be in the uncus, whereas that for taste is in the region of the insula. Seizures which have olfactory or gustatory components tend to involve either one or the other of these sensations, but only rarely are both excited simultaneously. Magnus, Penfield, and Jasper[29] has suggested that the region of the island of Reil and the adjacent parts of the temporal lobe and uncus form a cortical area for Edingere's "oral sense." They suggested that the impulses for taste, smell, and oral tactile sensations converge in this region, and from it corresponding motor effects like mastication and salivation result. The findings of the present study extend this concept. Epileptic discharges in this region may evoke olfactory or gustatory experiences, rhinostomal sensations, salivation, or masticatory movements. Depending upon the pattern of excitation, these phenomena may occur in-

dividually or in varying combinations. To group all these events under the term "uncinate fit" is imprecise, since only one element is dependent upon discharge in the uncus. Jackson[1] was aware that the term implies an oversimplification, and wrote that use of it was based "on the hypothesis that the discharge lesions in these cases are made up of some cells, not of the uncinate group alone, but of some cells of different parts of a region of which this gyrus is part – a very vague circumscription, I admit – the uncinate region." For these reasons, it seems wiser to me to classify seizures arising in this region not by an anatomic term but by the clinical phenomena which characterize them.

Olfactory seizures may be classified into hallucinations and illusions. The hallucinations are further divided into undifferentiated or indescribable olfactory sensations, recognizable or "formed" olfactory hallucinations, and multisensorial hallucinations, of which olfactory phenomena are components. In some instances olfactory reminiscences or memories may be described. Olfactory illusions probably are more common than is recognized, and careful inquiry should reveal more examples of them.

Gustatory sensations seem less complex. They usually consist of crude hallucinatory experiences. There is no reason, however, to assume that the gustatory sense is strikingly different; therefore, complex gustatory hallucinations and gustatory illusions conceivably could occur.

Patients may describe rhinostomal sensations of burning, tingling, or prickling, possibly indicating discharges in a secondary cortical area for oral and nasal sensations since these often occur coincident with olfactory or gustatory experiences.

Signs of vegetative discharge frequently are associated with these seizures. This is not surprising. In primitive creatures the sense of smell is essential for survival; therefore, an interaction of these systems might be expected. Alterations in the internal milieu could shift and reorient olfactory activities; conversely, olfactory stimuli could call forth changes in the autonomic state. Smell also bears a relationship to affective states. Odors have a very ancient and powerful capacity to induce emotion. This is, of course, well known in respect to animals, but even among human beings the use of perfume attests to the strength of this relationship. Evidence that the frontotemporal region is the major cortical center for autonomic activities[33] and the demonstration by Williams[34] that the temporal lobe contains structures involved in affective behavior clarify this complex, shifting association of ictal phenomena.

Feindel and Penfield[35] have suggested that the periamygdaloid region is intimately involved in the maintenance of the normal conscious state. They have observed that seizure discharges arising in this area often are associated with behavioral automatisms. In the present study, almost half the patients experienced alterations of consciousness during their seizures. These alterations ranged from subjective difficulty in thinking through states of clouded consciousness to actual loss of responsiveness associated with confused and automatic behavior.

Many years ago Herrick[36] postulated that the rhinencephalon has important actions other than olfaction, and he suggested that "an important function . . . is to serve as a nonspecific activator for all cortical activities." Time has confirmed his judgment. To this region of the brain are brought a variety of impulses which supply information concerning the internal state of the organism and some aspects of the external environment. Adjoining areas are presumed to store memories of past experiences. From this confluence may arise complex patterns of neuronal activity which result in alterations of external orientation and simultaneous adjustments of the internal milieu. This region in turn does not function in isolation but, rather, as one of a series of systems which by their sustained effects generate general adaptive states and thus assist the total adjustment of the organism.

SUMMARY

1. The history of the concept of uncinate seizures is reviewed. Observations on 55 patients form the basis of this report.

2. Olfactory phenomena occurred most frequently, usually in the form of hallucinations. The hallucinations ranged from crude, unrec-

ognizable sensations of smell to complex multisensorial elaborations. In rare instances olfactory "reminiscences" and illusions are reported.

3. The uncus appears to be the cortical center for smell. In one patient necropsy revealed focal gliosis in the uncus.

4. Gustatory phenomena were limited to undifferentiated hallucinations of taste.

5. Twelve patients reported rhinostomal sensations consisting of burning, tingling, or crawling sensations in the nose, mouth, or throat. In the majority they were associated with olfactory or gustatory hallucinations.

6. Interictal or postictal illusions of smell or taste or, less commonly, hallucinations, are described by some patients.

7. The relationship of these phenomena to "dreamy states," ictal affect, and vegetative disturbances during seizures was analyzed. An attempt was made to extend the concept of the functions of this area to explain the association of these events.

REFERENCES

1. Jackson, J. H.: On asphyxia in slight epileptic paroxysms—on the symptomatology of slight epileptic fits supposed to depend on discharge-lesions of the uncinate gyrus. Lancet 1:79, 1899.
2. Jackson, J. H., and Stewart, Purves: Epileptic attacks with a warning of a crude sensation of smell and with the intellectual aura (dreamy state) in a patient who had symptoms pointing to gross organic disease of the right temporo-sphenoidal lobe. Brain 22: 534, 1899.
3. Sander, Wilh.: Epileptische Anfälle mit subjektiven Geruchs-Empfindungen bei Zerstörung des linken tractus olfactorius durch einen Tumor. Arch. Psychiat. 4:234, 1874.
4. Jackson, J. H.: On the scientific and empirical investigation of epilepsies. In: Selected Writings of John Hughlings Jackson [Edited by James Taylor], London, Hodder and Stoughton, Limited, 1931, vol. 1, pp. 162-273.
5. Jackson, J. H.: On temporary mental disorders after epileptic paroxysms. In: Selected Writings of John Hughlings Jackson [Edited by James Taylor], London, Hodder and Stoughton, Limited, 1931, vol. 1, pp. 119-134.
6. Gastaut, H., Roger, J., and Giove, C.: Troubles de l'olfaction, de la gustation et de l'appétit chez les épileptique psychomoteurs. Ann. Med.-psychol. 113: 177, 1955.
7. Lennox, W. G., and Cobb, Stanley: Epilepsy. XIII. Aura in epilepsy: A statistical review of 1,359 cases. Arch. Neurol. & Psychiat. 30:374, 1933.
8. Mills, C. K.: The cerebral centers for taste and smell and the uncinate group of fits: Based on the study of a case of tumor of the temporal lobe with necropsy. J.A.M.A. 51:879, 1908.
9. Wilson, S. A. K.: The Morison lectures on nervous semeiology, with special reference to epilepsy. Lecture II. Symptoms indicating increase of neural function. Brit. M. J. 2:50, 1930.
10. Gowers, W. R.: The Hughlings-Jackson lecture on special sense discharges from organic disease. Brain 32:303, 1910.
11. Kennedy, Foster: The symptomatology of temporosphenoidal tumors. Arch. Int. Med. 8:317, 1911.
12. Jackson, J. H., and Beevor, C. E.: Case of tumour of the right temporosphenoidal lobe bearing on the localisation of the sense of smell and on the interpretation of a particular variety of epilepsy. Brain 12: 346, 1889.
13. Penfield, Wilder, and Jasper, Herbert: Epilepsy and the Functional Anatomy of the Human Brain. Boston, Little, Brown and Company, 1954, 896 pp.
14. Cushing, Harvey: The field defects produced by temporal lobe lesions. Brain 44:341, 1922.
15. Buzzard, Thomas: Two cases illustrating points in the diagnosis of tumour or other lesion of the uncinate region of the temporo-sphenoidal lobe. Lancet 1: 1807, 1906 .
16. Hamilton, A. M.: On cortical sensory discharging lesions (sensory epilepsy). New York State M. J. 35:575, 1882.
17. Worcester: Cited by Mills, C. K.: Cerebral localisation in its practical relations. Brain 12:358, 1889.
18. Jackson, J. H., and Colman, W. S.: Case of epilepsy with tasting movements and "dreamy state"—very small patch of softening in the left uncinate gyrus. Brain 21:580, 1898.
19. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms, and Treatment. New York, William Wood and Company, 1881, 255 pp.
20. Shenkin, H. A., and Lewey, F. H.: Taste aura preceding convulsions in a lesion of the parietal operculum (case report). J. Nerv. & Ment. Dis. 100:352, 1944.
21. Jackson, J. H.: Lectures on the diagnosis of epilepsy. In: Selected Writings of John Hughlings Jackson [Edited by James Taylor], London, Hodder and Stoughton, Limited, 1931, vol. 1, pp. 276-307.
22. Clarke, J. M.: Epileptic attacks preceded by subjective auditory and taste sensations, probably due to a tumour of the left temporo-sphenoidal lobe. Lancet 1:1119, 1900.
23. Spiller, W. G.: Remarks on the uncinate group of fits, and on severe subcutaneous hemorrhage occurring in epilepsy. Am. Med. 7:474, 1904.
Börnstein, W. S.: Cortical representation of taste in man and monkey. I. Functional and anatomical relations of taste, olfaction, and somatic sensibility. Yale J. Biol. & Med. 12:719, 1939-1940.
25. Bennett, Hughes: Discussion. Lancet 1:381, 1889.
26. Anderson, James: On sensory epilepsy: A case of basal cerebral tumour, affecting the left temporosphenoidal lobe, and giving rise to a paroxysmal tastesensation and dreamy state. Brain 9:385, 1886.
27. Frazier, C. H., and Rowe, S. N.: Certain observations upon the localization in fifty-one verified tumors of the temporal lobe. A. Res. Nerv. & Ment. Dis., Proc. 13:251, 1934.
28. Spillane, J. D.: Clinical investigation of olfactory function in brain tumour patients. Brain 62:213, 1939.
29. Magnus, Otto, Penfield, Wilder, and Jasper, Herbert: Mastication and consciousness in epileptic seizures. Acta psychiat. et neurol. scandinav. 27:91, 1952.
30. Jackson, J. H.: On a particular variety of epilepsy ("intellectual aura"), one case with symptoms of organic brain disease. Brain 11:179, 1888.
31. Weil, A. A.: Ictal depression and anxiety in temporal lobe disorders. Am. J. Psychiat. 113:149. 1956.
32. Daly, David: Ictal affect—part of a symposium on the psychophysiology of temporal lobe structures read at the meeting of the American Psychiatric Association, Chicago, Illinois, May 13 to 17, 1957.
33. Mulder, D. W., Daly, David, and Bailey, A. A.: Visceral epilepsy. Arch. Int. Med. 93:481, 1954.
34. Williams, Denis: The structure of emotions reflected in epileptic experiences. Brain 79:29, 1956.
35. Feindel, William, and Penfield, Wilder: Localization of discharge in temporal lobe automatism. Arch. Neurol. & Psychiat. 72:605, 1954.
36. Herrick, C. J.: The functions of the olfactory parts of the cerebral cortex. Proc. Nat. Acad. Sc. 19:7, 1933.

Unusual form of cerebellar ataxia with sex-linked inheritance

Nathan Malamud, M.D. and Peter Cohen, M.D.

THE DIFFICULTIES encountered in classification of the hereditary ataxias are well known. In spite of attempts by Greenfield[1] to clarify the problem in a recent monograph, cases continue to present themselves that are impossible to fit into any scheme.

The following heredofamilial condition is reported for a number of reasons: 1) the rare sex-linked characteristic of its mode of inheritance, 2) the constant changes in the neurologic picture as the disease progressed, and 3) the unusual localization of the pathoanatomic changes.

CASE REPORTS

Case 1. A male child was first seen in the outpatient department of the University of California Hospital at the age of two years and four months, because he was unable to walk, talk, or control his extremities. His parents were unaware of any similar disorders in the family. Birth was uneventful and his early development was normal until the age of ten months when he fell from a grocery store basket and landed on the back of his head but did not lose consciousness. Shortly afterward, it was noted that first his hands and later his feet quivered during waking hours and that his left eye tended to turn in. On admission to a local hospital, a pneumoencephalogram and examination of the cerebrospinal fluid were within normal limits, but an electroencephalogram revealed evidence of a focal lesion in the left hemisphere. At the age of two years he was again hospitalized. At this time he was unable to stand alone but, with support, stood on a wide base. There was marked ataxia of the upper and lower extremities. An occasional head tremor was noted. The knee jerk on the left side was increased and was associated with a positive Babinski sign. There were external rectus weakness on the left and bilateral papilledema. Because of suspicion of a posterior fossa tumor, a ventriculogram was performed which revealed "normally filled ventricles without dilatation or shift." Following ventriculography, the papilledema subsided. He received a course of radiation therapy without definite benefit.

Examination at the University of California Hospital confirmed the marked ataxia and sixth nerve palsy on the left. The optic disks were noted to be flat and pale. A psychometric test found him to be functioning at about the 12 to 15 month level at a chronological age of two years and five months. Subsequent repeated examinations revealed slowly progressive deterioration in both motor and mental abilities. At the age of three years he exhibited spasticity of his legs for the first time, and the head tremor which had been present became more pronounced. By the age of six and one-half years he was unable to do anything but lie in bed in a decerebrate posture. He had a mask-like expressionless face, showed evidence of marked extrapyramidal rigidity in all extremities, and had a tremor that persisted on voluntary motion. He was incontinent of urine and feces. His final admission to the hospital occurred at the age of seven years when, following administration of an enema at home, he suddenly became blue and limp. While in the hospital he developed convulsions during periods of apnea and expired two days later, in spite of treatment. The approximate duration of his illness was six years.

Postmortem examination. The general autopsy findings were pulmonary congestion, pneumonitis, patchy atelectasis, mild chronic cystitis, and pyelitis.

The brain weighed 1,130 gm. The convolutions were well outlined and there were no abnormalities in the leptomeninges or blood vessels. The cerebellum was severly atrophied and with the medulla and lower pons it weighed 92 gm. Coronal sections showed no evidence of cerebral atrophy, and the lateral and third ventricles were of normal size. Small cysts of 1 or 2 mm. in size were scattered in the caudate nucleus, putamen, thalamus, and tectum. All folia of the cerebellum were atrophic and the dentate nuclei were shrunken and indistinct. The inferior olives were pale and the fourth ventricle was considerably dilated. There was no visible atrophy of the pons, brachium pontis, or pyramids.

Microscopically, there was evidence of a primary degenerative process restricted to several anatomic systems. Histologically, the changes were characterized by dropping out of nerve cells, shrinkage and hyperchromatosis of those remaining, and increase in reacting microglia, astroglia, and glial fibers. The small cysts were focal areas

From the departments of psychiatry (neuropathology) and pediatrics, University of California School of Medicine, San Francisco, California.

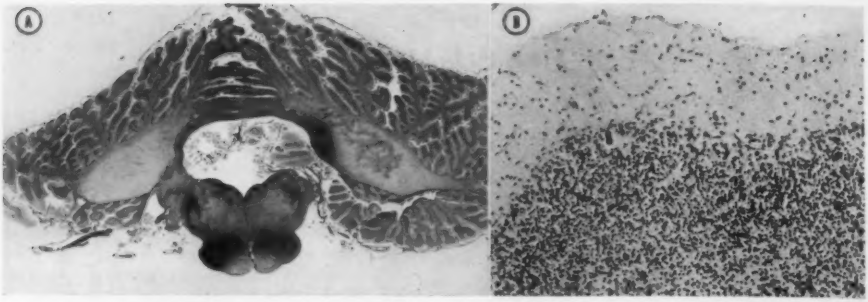


FIG. 1. *A*, cerebellum and medulla showing diffuse atrophy and gliosis of folia, dentate nuclei, inferior olives, olivocerebellar fibers, and vestibular nuclei (artifacts in white matter of cerebellum). Holzer stain. *B*, cerebellum showing disappearance of Purkinje cells and reactive gliosis in Bergmann and molecular layers. Nissl stain.

of necrosis that underwent reparative gliosis intermingled with vascular proliferation.

The lesions were distributed in the following regions:

Cerebellum and its connections. In Holzer preparations (figure 1A), gliosis was demonstrated in all folia of the cerebellum (somewhat more marked in superior than inferior parts), dentate nuclei, superior peduncles, inferior olives, inferior peduncles, and vestibular nuclei; there was relatively little gliosis in the central white matter. In the gray matter of the cerebellum (figure 1B), the Purkinje cells had virtually disappeared, accompanied by increased glia in the Bergmann and molecular layers, while the granular layer remained intact. The dentate nucleus exhibited equally severe degeneration of its neurons, associated with diffuse micro- and macroglia reaction (figure 2A), while its fleece and hilus showed dense gliosis (figure 2B). This could be followed throughout the course of the brachium conjunctivum. There was marked involvement of the inferior, dorsal, and medial accessory olives. In the inferior olive a completely destroyed dorsal part contrasted with a better preserved ventral part (figure 3A and B). Olivocerebellar, interolivary, and external arcuate fibers showed secondary degeneration. The vestibular nuceli were more moderately affected.

Red nucleus, thalamus, basal ganglia, and optic tracts. Diffuse bilateral gliosis was demonstrated with the Holzer method in the red nucleus, thalamus, corpus Luysi, globus pallidus, and optic tract (figure 4A and B). In the red nucleus there was marked paucity of neurons and proliferation of glial elements that stood out in sharp contrast with an intact substantia nigra (figure 5A). There was widespread degeneration throughout all nuclear groups of the thalamus, leaving intact only isolated nests of neurons (figure 5B). The globus pallidus and the corpus Luysi showed diffuse degeneration and gliosis, although of moderate degree. The caudate nucleus and putamen contained only a few circumscribed lesions (figure 5C). There was diffuse gliosis throughout the course of both optic tracts. There were no changes in other parts of the brain, with the exception of acute anoxia in neurons of the cerebral cortex apparently caused by the terminal convulsions. The spinal cord was not examined.

Several months following the death of case 1, his mother reported that her sister's child was showing similar symptoms and he was

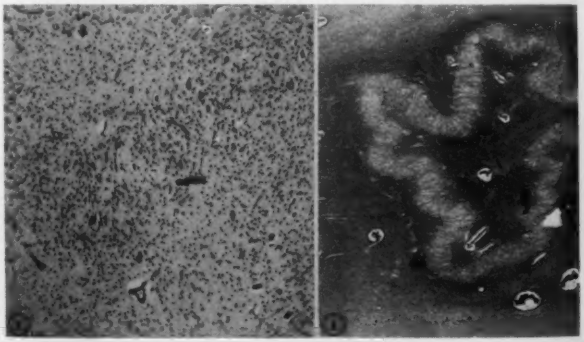


FIG. 2. Dentate nucleus showing in *A*. Paucity of neurons and proliferation of micro- and macroglial nuclei, Nissl stain. *B*, dense gliosis of the white matter within and around it. Holzer stain.

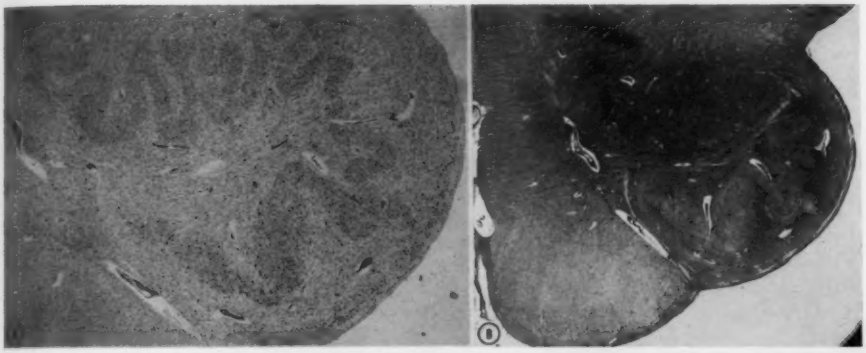


FIG. 3. *A*, inferior olive in which degeneration of dorsal part contrasts with relative preservation of ventral part. Nissl stain. *B*, corresponding gliosis in parts of inferior olive; also gliosis of accessory olives. Holzer stain.

therefore admitted to the University of California Hospital for evaluation.

Case 2. A three and one-half year old boy had a normal birth and development until the age of 16 months. At this time it was noticed that, although he had previously learned to walk, he now began to stumble and fell frequently, developed tremors of his arms, and the left eye deviated medially. At the age of two years and ten months, he began having attacks characterized by a quivering voice and rapid tremors of left hand and forearm, but without loss of consciousness. His condition progressed further so that by the time of admission he was unable to speak beyond a word or two and got around only by crawling.

Examination disclosed marked ataxia, intention tremor of hands, and medial deviation of the left eye but no sign of optic atrophy. He was awarded a mental age of 20 to 22 months at the chronologic age of three years and six months. A pneumoencephalogram showed dilatation of the fourth ventricle and basal cisterns consistent with cerebellar atrophy. An electroencephalogram revealed generalized paroxysmal dysrhythmia of nonspecific type, consisting of bursts of high voltage spiking and irregular asynchronous sinusoidal slow waves of 3 to 6 c.p.s., with focal change in the frontal and precentral area on the left.

Although the "myoclonic" attacks are fairly well controlled at the present time, the child's condition has continued to deteriorate, with development of bilateral internal strabismus, loss of facial expression, and increased muscle tone in the left arm.

Additional family history. Following discovery of the second case, the maternal grandmother was able to obtain from her own mother, who was still living, information concerning other instances of the disease in the family, as outlined in figure 6. The pedigree becomes intelligible if it is assumed that the mother of the three siblings in I was normal, but carried in one of her two X chromosomes a recessive abnormal gene, d. Her two daughters received the abnormal d in their maternal X chromosomes but a dominant normal gene D in the X chromosome from their father. Excluding II-2 who died in infancy, the two daughters jointly had six affected and two normal

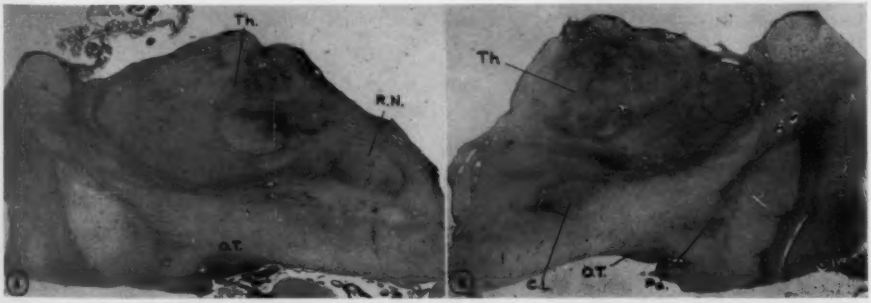


FIG. 4. *A*, gliosis of thalamus, red nucleus, and optic tract on left side. *B*, gliosis of thalamus, corpus Luysi, globus pallidus, and optic tract on right side. Holzer stain.

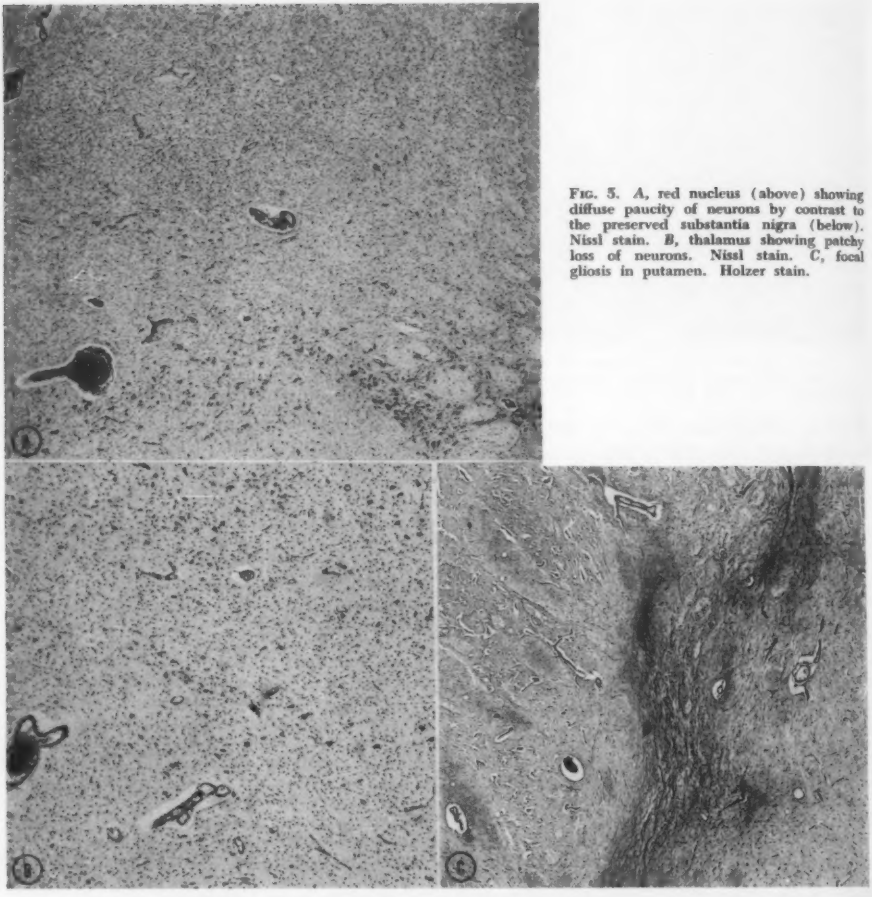


FIG. 5. *A*, red nucleus (above) showing diffuse paucity of neurons by contrast to the preserved substantia nigra (below). Nissl stain. *B*, thalamus showing patchy loss of neurons. Nissl stain. *C*, focal gliosis in putamen. Holzer stain.

sons, a permissible deviation from the expected 4:4 ratio. Among the eight sisters of these males, some should have been free from the abnormal gene, DD, and others should be carriers again, Dd. The latter was apparently true for II-14, since affected grandsons appeared among her offspring. A definite decision regarding the constitution of the other female descendants of I-1 and I-3 is impossible, since the number of normal children and grandchildren produced by them is too limited. The females III-8 and III-11 are Dd, as revealed by the presence of their affected sons IV-3 and IV-4, respectively. Each of the daughters IV-5 and IV-6 have a 50 per cent chance of being Dd carriers.

DISCUSSION

Genetic Features

The transmission of the disease is best explained by the assumption of a recessive gene in the X chromosome. The two most obvious alternatives, namely ordinary autosomal dominant and recessive inheritance, are excluded for the following reasons. Dominant inheritance is contraindicated by the fact that all parents of affected individuals are normal, although one of the parents would have to carry the dominant gene. Recessive inheritance is excluded, since it would require both

parents of all four families in which affected individuals appear to have been heterozygous for the recessive gene. Considering the extreme rarity of the disease, it cannot be assumed that four different "outside" spouses were carriers. Furthermore, both ordinary autosomal dominant or recessive types of inheritance are unlikely, since they do not account for the fact that all eight affected individuals are males.

In cases like this, in which the affected males are unable to produce children, an alternative genetic interpretation cannot be excluded. The trait could also be caused by a gene in an autosome which acts as a recessive in females and as a dominant in males. This explanation, however, is an unlikely one, since there is no reason to assume a sex-limited expression of a gene responsible for a degenerative brain disease. The prognosis of the genotype of normal individuals would be essentially alike in the case of a recessive sex-linked gene and a sex-limited autosomal gene.

The literature on the hereditary ataxias contains extremely few reports of sex-linked inheritance. In a family with symptoms of spinal ataxia of the Roussy-Lévy type, Popow[2] found that the disease was limited to males but was transmitted either through affected males or unaffected females. In a family of Friedreich's ataxia reported by Turner and Roberts,[3] only males were affected and the disease was transmitted by females. Van Bogaert and Moreau[4] reported a family with combined features of Charcot-Marie-Tooth's disease and Friedreich's ataxia in which the disease was transmitted as a sharply sex-linked inheritance. Pappworth and O'Mahoney[5] described in three brothers a sex-linked familial syndrome characterized by cerebellar signs, pes cavus, claw hands, Charcot-Marie-Tooth form of muscle atrophy, obesity of trunk and face, and premature arcus senilis. The present report is the only one known of sex-linked inheritance in a predominantly cerebellar disorder.

Clinical Features

The chief clinical manifestations in our two cases were initial cerebellar signs of ataxia, dysarthria, and intention tremor that were gradually replaced by extrapyramidal signs. There were signs of mental deterioration in both cases, and optic atrophy in case 1 and probable myoclonus epilepsy in case 2.

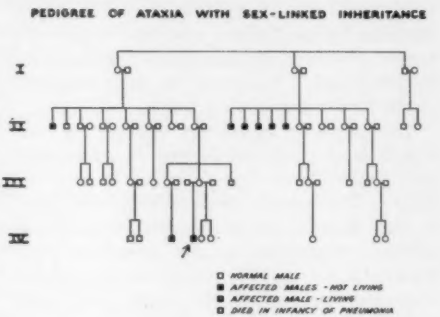


FIG. 6. Propositus. The person through whom the pedigree became known marked with arrow. Only the affected individuals in IV had been seen by the authors. The order of birth in I and II and III is not known.

The association of cerebellar and extrapyramidal signs has been commonly observed in cases of cerebellar ataxia. Rosenhagen[6] reviewed the literature and found, out of a total of 45 cases, 25 with extrapyramidal signs. In the majority of these, the author was able to find lesions either in the substantia nigra or basal ganglia to which he attributed the extrapyramidal rigidity and involuntary movements, respectively. In our case 1 there were lesions in the corpus Luysi, globus pallidus, and striatum to account for similar signs. There is apparently a common vulnerability of the two systems to the same noxious influences, although the latter remain obscure.

Dementia or mental defect, as pointed out by Greenfield,[1] is a not infrequent symptom in cases of spinal and cerebellar ataxia. Its underlying pathoanatomic substrate has not always been established, however. In some cases changes in the cerebral cortex have been reported. In our case 1 the latter was not involved, but the thalamus was severely degenerated. It is suggested that thalamic pathology can produce mental defect or deterioration directly, since in some cases with severe retardation it is the only demonstrable lesion.[7]

Optic atrophy has been frequently observed in various forms of hereditary ataxia. According to Bell and Carmichael,[8] it is characterized by gradual onset and by lack of evidence of sex linkage, in contrast with Leber's hereditary optic atrophy. In our case 1 the optic

involvement was of rapid onset so that it was mistaken for papilledema associated with brain tumor. However, it has not been demonstrated in case 2 and its occurrence in other members of the family remains unknown.

The probable myoclonus epilepsy of our case 2 is of particular interest in connection with the syndrome first described by Ramsay Hunt.[9] The dentato-rubral involvement found in this disorder is, in the opinion of some authors, responsible for the myoclonus epilepsy. In our case 1, the dentato-rubral involvement was one of the most conspicuous lesions. But although myoclonus was not described in case 1, its presence in case 2, where the pathology may be assumed to be similar, is worthy of mention.

Pathoanatomic Features

An outstanding feature of the disorder was the unusual distribution of lesions in case 1, both within and outside the cerebellar system. In the latter a combination of cerebello-olivary and dentato-rubral degeneration occurred, whereas the pontocerebellar connections were spared (unfortunately the spinal cord was not examined). Such a distribution of lesions in the cerebellar ataxias is rare.[1] The lesions outside the cerebellar system, namely those in the corpus Luysi, thalamus, basal ganglia, and optic tracts, are also rarely combined or associated with the cerebellar changes.* These findings serve to emphasize the unpredictable combination of lesions that may be encountered in the group of the heredodegenerative disorders.

SUMMARY

1. An unusual form of hereditary cerebellar ataxia in two children is reported, one with postmortem findings.

2. The mode of inheritance was sex-linked recessive.

3. The outstanding clinical features were a gradual change from an initial cerebellar to an extrapyramidal syndrome, to which there were corresponding lesions in the two systems.

*For a detailed discussion of this problem see: J. K. Smith, V. E. Gonda, and N. Malamud: Unusual form of cerebellar ataxia. Neurology. In press.

The authors are indebted to Dr. Curt Stern, professor of zoology, University of California in Berkeley for his analysis of the genetic findings.

REFERENCES

1. Greenfield, J. G.: The Spino-Cerebellar Degenerations. Charles C Thomas, Springfield, Illinois, 1954.
2. Popow, A.: Une famille atteinte d'une forme particulière de maladie héréditaire (Roussy-Lévy). Rev. neurol. 2:447, 1932.
3. Turner, E. V., and Roberts, E.: A family with sex-linked hereditary ataxia. J. Nerv. & Ment. Dis. 97:74, 1938.
4. Van Bogaert, L., and Moreau, M.: Combinaison d'amyotrophie de Charcot-Marie-Tooth et de la maladie de Friedreich. L'Encèphale 34:312, 1939.
5. Pappworth, M. H., and O'Mahoney, P. F.: An unusual familial cerebellar syndrome. J. Nerv. & Ment. Dis. 119:437, 1954.
6. Rosenhagen, H.: Die primäre Atrophie des Brückenfusses und der unteren Oliven. Arch. Psychiat. 116: 163, 1943.
7. Malamud, N.: Status marmoratus. J. Pediat. 37: 610, 1950.
8. Bell, J. M., and Carmichael, E. A.: On hereditary ataxia and spastic paraplegia. Treasury of Human Inheritance 4: part 3, 1939.
9. Hunt, J. R.: Dyssynergia cerebellaris myoclonica. Brain 44:490, 1921.

■ Mental symptoms, when discovered, do not by themselves point to *tumour*. They are, indeed, not symptoms of any *one* sort of pathological process, but symptoms of loss of the most special sensori-motor processes by *any* kind of *slow* pathological change. They point of necessity to the cerebral hemisphere as the part affected by the tumour. But, as we shall see, that part may, as in cases of tumor of the cerebellum, be affected in a very indirect way. There is in tumour of the middle lobe of the cerebellum obstruction to return of blood by the veins of Galen: as a consequence of this there is effusion into the ventricles, and hence squeezing of the cerebral hemisphere.

J. Hughlings Jackson in *Lectures on the Diagnosis of Tumours of the Brain*, published in 1872.

Effect of methylphenidate hydrochloride in antagonizing barbiturate-induced depression

Howard Ticktin, M.D., Jerome Epstein, M.D.,
James G. Shea, M.D. and Joseph F. Fazekas, M.D.

THE TREATMENT of central nervous system depression induced by the ingestion of barbiturates is a problem not infrequently encountered in clinical practice. Although there are many analeptic agents currently available for such purposes, their efficacy, with the possible exception of pentylenetetrazol and picrotoxin,[1] is questionable. In fact, there are some who believe that the use of such drugs may even be harmful and advocate only good symptomatic care and dialysis, when necessary, as the treatment of choice for deep barbiturate intoxication.[2] Recently a new analeptic agent, methylphenidate hydrochloride (Ritalin), has been reported to be of therapeutic value in barbiturate-induced depression.[3] In this study, findings concerning its effectiveness in overcoming self-induced barbiturate depression, as well as its influence on cerebral hemodynamics and oxygen consumption in subjects to whom various dosages of amobarbital were administered, are presented.

METHOD

Clinical observations were made in 11 patients admitted to the hospital because of varying degrees of central nervous system depression due to self-administration of undetermined amounts of barbiturates, often with suicidal intent. Seven of these subjects were deeply sedated, could not be aroused, and responded to noxious stimuli only with purposeless movements. The remaining four subjects were comatose, with depression of vital signs. Methylphenidate hydrochloride in doses ranging from 30 to 1,400 mg. was administered intravenously to these subjects.

A second experimental group consisted of nine convalescent hospitalized subjects in whom cerebral function studies were performed one-half to one hour after the intravenous administration of 250 to 1,700 mg. of sodium amobarbital. The amount of drug administered was governed by the induction of a state of unconsciousness sufficiently deep so that the subjects responded only reflexly to noxious stimuli. This state did not necessarily persist without spontaneous changes before the first cerebral studies were performed. Cerebral function studies were repeated within five minutes following the rapid intravenous administration of methylphenidate hydrochloride and from one-half to one hour after initial studies were performed. In all of these subjects, barbiturate levels were determined just prior to methylphenidate hydrochloride administration.

Scheinberg and Stead's modification[4] of the Kety and Schmidt procedure[5] for the determination of cerebral blood flow (CBF) was applied in this study. Blood oxygen was determined by the manometric technic of Van Slyke and Neill.[6] Mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer.[7] Goldbaum's method was used for the estimation of blood barbiturate levels.[8]

RESULTS

Table 1 presents the clinical observations on the effectiveness of methylphenidate hydrochloride in arousing patients hospitalized because of self-induced barbiturate intoxication. In eight of the 11 subjects, awakening was noted following the administration of varying

From the George Washington University Hospital and the District of Columbia General Hospital, Washington, D.C.
This study was supported in part by a research grant (PHS B-178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

TABLE 1

EFFECT OF RITALIN* ON SELF-INDUCED BARBITURATE DEPRESSION

Subject	Age	Drug	Amount of Drug (mg.)	Time Prior to Therapy (hours)	Clinical Status on Admission	Ritalin Dose Intravenous (mg.)	Results
1	26	Seconal	1,500	18	Deeply sedated, reflexes normal	50	In 5 min. able to sit and converse; remained awake
2	33	Seconal	?	?	Comatose, areflexic	250	No change in consciousness; respiratory rate increased; B.P. rose from 90/80 to 140/110
3	37	Phenobarb.	1,500-2,000	?	Deeply sedated, reflexes depressed	50	In 3 min. opened eyes; able to converse; remained awake
4	53	Nembutal	1,500	4	Deeply sedated, reflexes depressed	100, followed by 100 in 500 cc. isotonic saline	In 2 min. awake; able to converse; remained awake
5	35	Seconal	1,800	?	Deeply sedated, reflexes normal	30	Aroused within 2-3 min.; able to converse
6	53	Tuinal	2,400	4	Comatose, areflexic	50, followed by 50	No change in consciousness. B.P. rose from 80/60 to 120/70. After 2nd dose, no change in consciousness. Reflexes returned; responded to noxious stimuli
7	23	Tuinal	?	3	Deeply sedated, reflexes depressed	90, followed by 60 in 300 cc. isotonic saline	Aroused, lethargic. B.P. rose from 90/75 to 110/75. Became alert during infusion
8	66	Seconal	1,800	2	Comatose, fixed dilated pupils	100, followed by 250 in 250 cc. dextrose in water	Remained comatose but responded to noxious stimuli; pupils constricted and reacted to light; lethargic at end of infusion
9	28	Butibel	?	?	Deeply sedated, reflexes depressed	30	In 4 min. aroused and able to converse
10	32	Amytal	2,000	12	Deeply sedated, reflexes depressed	400, followed by 500 in 400 cc. dextrose in water	In 20 min. lethargic, reflexes normal. At termination of infusion, awake and conversing
11	40	Nembutal	1,500	6-8	Comatose, reflexes markedly depressed	400, followed by 1000 in 400 cc. dextrose in water	In 5 min. B.P. rose from 80/60 to 110/80. Swallowed spontaneously, reflexes increased. After infusion, awake and conversing

*Ritalin is the trade-marked name for methylphenidate hydrochloride.

TABLE 2

INFLUENCE OF SODIUM AMYTAL AND RITALIN ON CEREBRAL HEMODYNAMICS AND METABOLISM

TABLE 2

INFLUENCE OF SODIUM AMYTAL AND RITALIN ON CEREBRAL HEMODYNAMICS AND METABOLISM

Subject	Age	CBF		$CMRO_2$		CVR		MAP		Amytal Level		Dose of Amytal (Mg.)	Dose of Ritalin (Mg.)	Clinical State After Amytal	Response to Ritalin
		C	E	C	E	C	E	C	E	C	E				
1	37	49.7	45.8	2.9	2.4	1.6	2.1	81	96	3.8	2.4	500	100	Responded to pain	None
2	56	71.8	64.2	1.7	2.7	1.5	1.9	106	125	5.8	4.3	325	200	Unresponsive	None
3	62	31.2	30.4	1.0	1.3	2.3	2.5	73	77	14.7	11.7	1000	200	Unresponsive	None
4	63	32.8	26.6	2.2	2.1	2.5	2.7	81	71	3.2	2.0	300	200	Somnolent	None
5	16	90.4	67.6	2.1	2.2	0.7	1.2	59	80	20.0	15.5	1500	400	Unresponsive	None
6	72	29.2	25.6	2.1	2.2	2.7	3.4	78	88	8.5	7.0	250	100	Responded to pain	None
7	76	50.5	47.4	2.0	2.7	1.7	2.3	88	111	11.0	7.6	600	100	Responded to pain	From sleeping state, awake and talking
8	66	41.9	33.0	2.4	2.7	2.1	3.3	89	109	1.7	1.0	780	200	Responded to pain	None
9	38	38.9	21.3	1.5	1.1	2.0	3.2	76	69	33.3	30.2	1700	1000	Unresponsive	None
Mean Values	54	48.5	40.2*	2.0	2.2	1.9	2.5*	81	92*	11.3	9.1	717	278		

*Significant difference, $p < .05$

CBF indicated cerebral blood flow in cubic centimeters/minute/100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cubic centimeters/minute/100 gm. of brain; CVR, cerebral vascular resistance in millimeters of Hg/cubic centimeters of blood/minute/100 gm. of brain; MAP, mean arterial blood pressure in millimeters of Hg; C, values obtained after Amytal administration, and E, after Ritalin administration.

amounts of methylphenidate hydrochloride (30 to 1,400 mg.); arousal was immediate and permanent. In three subjects there was either no significant response or only some medullary stimulation, as evidenced by increased respiratory rate or rise in blood pressure.

Table 2 presents the cerebral hemodynamic and metabolic findings in nine subjects to whom varying concentrations of sodium Amytal were administered followed by varying dosages of methylphenidate hydrochloride. Since control observations prior to the administration of sodium Amytal were not made, it is difficult to determine precisely the effects of this drug alone on cerebral hemodynamics and metabolism. The mean value of 2.0 cc. for cerebral oxygen consumption after sodium Amytal administration is significantly reduced from normal values and confirms previous observations that this drug exerts an inhibitory effect on cerebral oxidative reactions. The mean values for cerebral blood flow, vascular resistance, and mean arterial pressure were not appreciably altered by the barbiturate.

The mean values obtained after methylphenidate hydrochloride administration demonstrate a significant reduction in cerebral blood flow ($p < .05$), an increase in cerebral vascular resistance and mean arterial pressure, but no change in cerebral oxygen consumption. The explanation for the slight reduction in cerebral blood flow observed is not readily apparent. The increase of cerebral vascular resistance could be anticipated in view of the associated elevation of mean arterial pressure and would not account for the reduction in cerebral blood flow. The failure of methylphenidate hydrochloride to influence total cerebral oxygen may explain its ineffectiveness in influencing the state of consciousness in these patients.

Barbiturate levels in these subjects ranged from 1.7 to 33.3 micrograms per ml. one-half to one hour after the administration of Amytal, and fell spontaneously by 0.7 to 4.5 micrograms per ml. approximately 30 minutes later. The latter effect can hardly be attributed to methylphenidate hydrochloride administration and probably reflects elimination of the drug.

DISCUSSION

It will be noted from the data presented that there was no correlation between blood

barbiturate level and the degree of central nervous system depression in the experimental subjects. This observation is probably related to the difference in dosage of the barbiturate required to produce approximately the same initial effect and points out the rather marked variation in susceptibility to the drug. The physiologic explanation for this finding is not apparent, but may be related to differences in permeability of the blood brain barrier or barbiturate-binding capacity of various tissues or perhaps directly related to the vulnerability of the cerebral enzyme systems depressed by the barbiturates. It is somewhat surprising that only one of the experimental group showed significant awakening after administration of methylphenidate hydrochloride, while a considerably greater number of the group under clinical observation were responsive. In the subjects aroused, the degree of barbiturate depression may not have been marked, and any of the many analeptics given in adequate concentrations may well have awakened the subjects. It should also be emphasized that in this population it is practically impossible to accurately ascertain the dose of barbiturate ingested or the time of its ingestion, and, therefore, it is difficult to evaluate the clinical effectiveness of any analeptic.

Undesirable side effects were not noted on intravenous doses as large as 900 mg. given over a one-hour period. As our clinical experience with this drug increased, it became apparent that larger doses of the drug were safe and more effective than the doses used earlier. The small doses given may account for the lack of response noted in several of the clinical subjects. The fact that doses as large as 1,400 mg. were tolerated by the subjects previously depressed by sodium Amytal indicated that pharmacologic antagonism must exist between these two drugs. In several subjects not receiving sodium Amytal and given 200 to 300 mg. of methylephenidate hydrochloride intravenously, psychomotor activity was markedly increased and the patients became extremely apprehensive and tremulous.

It may be significant to note that methylphenidate hydrochloride has been reported to reverse readily the subcortical depression induced by Promazine[9] and that the excitation induced by methylphenidate hydrochloride previously referred to was immediately controlled by the administration of Promazine. On this basis it would seem reasonable to deduce that methylphenidate hydrochloride may act primarily on the subcortical centers by stimulating subcortical activity. In the case of moderate barbiturate sedation, it may overcome cortical depression. In heavier barbiturate sedation, methylphenidate hydrochloride may not sufficiently activate subcortical areas so that the more deeply depressed cortex could respond to increased centripetal bombardment. In this regard, it may be pertinent to note that both light barbiturate depression[10] and sedation by the phenothiazine derivatives[11] appear to be due to inhibition of adenosinetriphosphate utilization or breakdown rather than to oxidative inhibition.

In large doses methylphenidate hydrochloride, even in the heavily sedated patient, may exhibit some vasopressor and respiratory stimulant action, suggesting that it may also affect medullary centers. This should not be surprising in view of the fact that barbiturates are recognized to cause a descending depression of the neuroaxis; with large doses medullary centers might be expected to show at least some responsiveness to an analeptic.

In view of the finding that methylphenidate hydrochloride appears to be effective in reversing moderate barbiturate sedation and since undesirable side-effects (convulsions) have not been observed following the administration of large concentrations of this drug to patients previously given barbiturates, it would seem that it has therapeutic value, particularly in those cases with moderate central nervous system depression.

SUMMARY AND CONCLUSIONS

Methylphenidate hydrochloride was administered to 11 subjects who were hospitalized because of self-administration of barbiturates and to nine subjects who were given 250 to 1,700 mg. of sodium amobarbital intravenously. Eight of the former group and one of the latter showed clinical awakening. Cerebral studies in the subjects given amobarbital showed no increase in cerebral oxygen consumption after methylphenidate hydrochloride administration. Methylphenidate hydrochloride appears to have limited therapeutic value in deep

barbiturate sedation, but it may be valuable in the therapy of moderate barbiturate depression.

The technical assistance of William K. Young, Marie D. Negron, and Julia V. V. Johnson is gratefully acknowledged.

REFERENCES

1. Koppanyi, T., and Fazekas, J. F.: The use of correctives in the prevention of barbiturate intoxication. Am. J. M. Sc. 226:597, 1953.
2. Eckenhoff, J. E., and Dam, W.: The treatment of barbiturate poisoning with or without analeptics. Am. J. Med. 20:912, 1956.
3. Carter, C. H.: The effects of reserpine and methylphenidylacetate (Ritalin) in mental defectives, spastics and epileptics. Psychiatric Research Report of A.P.A. 4:44, 1956.
4. Scheinberg, P., and Stead, E. A., Jr.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. J. Clin. Investigation 28:1163, 1949.
5. Kety, S. S., and Schmidt, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. J. Clin. Investigation 27:476, 1948.
6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Methods. Baltimore, Williams & Wilkins Company, 1932, pp. 321.
7. Alman, R. W., and Fazekas, J. F.: Apparatus for continuous blood-pressure observation. New England J. Med. 248:105, 1953.
8. Goldbaum, L. R.: Determination of barbiturates. Anal. Chem. 24:1604, 1952.
9. Ehrmantraut, W. R., Shea, J. G., Ticktin, H. E., and Fazekas, J. F.: Influence of Promazine and methylphenidate on cerebral hemodynamics and metabolism. Arch. Int. Med. 100:66, 1957.
10. Bain, J. A.: Enzymatic aspects of barbiturate action. Federation Proc. 2:653, 1952.
11. Grenell, R. G., Mendelson, B. A., and McElroy, W. D.: Effects of chlorpromazine on metabolism in central nervous system. Arch. Neurol. & Psychiat. 73: 347, 1955.

Hippocrates, in his book concerning the glands, says that the brain is like a gland, and that humours flow from it, which, if free in their course, purify the brain; but if restrained or obstructed, give occasion to various diseases. These humours, he asserts, sometimes become acrid and corrosive, producing much disturbance in the system, with derangement of mind, and convulsions of the brain, which affect the whole body. He considers the brain as an organ of great consequence and power in the human frame; but his notions of its structure are very indistinct: he calls it, however, the seat of sense and intelligence. It is by this, he says, chiefly, that we think, and understand, and see, and hear, and know what is base and honourable, evil and good, pleasant and unpleasant, &c. And again, The brain is the messenger or instrument of the intellect.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Distribution of cutaneous hyperalgesia

Gerald H. Klingon, M.D.* and William H. Jeffreys, M.D.**

THE PROBLEM explored in this study is suggested by the distribution of deep pain and cutaneous sensory patterns commonly seen in cervical radiculopathy. Deep pain and cutaneous dysesthesias and numbness can often be traced to one or two spinal segments. Because deep pain and cutaneous sensory phenomena are usually not anatomically contiguous, their unitary relationship may at first appear somewhat tenuous. Therefore, an attempt was made to ascertain whether a predictable pattern of altered cutaneous sensation would emerge when deep pain in certain muscles was induced. As a corollary, an effort was made to determine whether cutaneous anesthesia would abolish induced deep pain in a segmentally predictable manner.

METHOD AND MATERIAL

A single subject, who was unacquainted with the problem, was used throughout. The Hardy-Wolff-Goodell apparatus was used to determine cutaneous perception. The Hardy-Wolff-Goodell apparatus, or dolorimeter, is an instrument for investigating the threshold or intensity of pricking pain. It provides a means of applying a measurable and controlled radiant heat stimulus. The stimulus is delivered through an aperature approximately one inch in diameter in a portable nozzle, which is applied to skin blackened with India ink. The radiant output of the instrument is adjusted by means of a heat-setting dial. The dial is calibrated from 50 to 500 millicalories per square centimeter per second, with calibration points every ten millicalories. A timer initiates the stimulus and controls the time of exposure by means of a button. The duration of exposure is set by a timing dial. The measurement of pain threshold is expressed as X millicalories if the exposure time is constant, and as X millicalories at Y seconds if both radiant heat output and exposure time are adjusted. Before each experiment a thermal stimulus was applied to various points in the upper extremity, which were first blackened with India ink. The subject was asked to respond to the stimulus on the following scale: If only heat was felt, it was to be reported as such. Minimal pricking was to be reported as threshold. If the intensity of the sensation was greater than threshold pricking, the stimulus was to be reported in grades 1, 2, 3, up to 10, that is, pain of increasing intensity reported by grades. Threshold was then determined for all the points stimulated. Following this 0.5 to 2 cc. of 5 per cent sodium chloride was injected into the selected muscle, after which the same points were again stimulated. The subject was then asked to respond according to the pain intensity scale. Subsequently, when the pain had disappeared, control stimulation was performed. If a discernible difference was noted between the experimental and the control studies, the result was considered significant.

RESULTS

In each instance the induction of moderately severe pain in a given muscle resulted in cutaneous hyperalgesia. The hyperalgesic points are indicated in the accompanying diagram (figure 1), together with symbols designating the painful muscle. It should be noted that the maps represent the known physiologic or total extent of each cutaneous segment. The dermatomes are derived from Foerster,[1] with the exception of the seventh cervical dermatome which is derived from Brock.[2] It can

From the Second (Cornell) Neurology Service, Bellevue Hospital, New York City.

*Present address: Memorial Center, New York City.

**United States Public Health Service clinical trainee, supported by a grant from the National Institute of Neurological Diseases and Blindness.

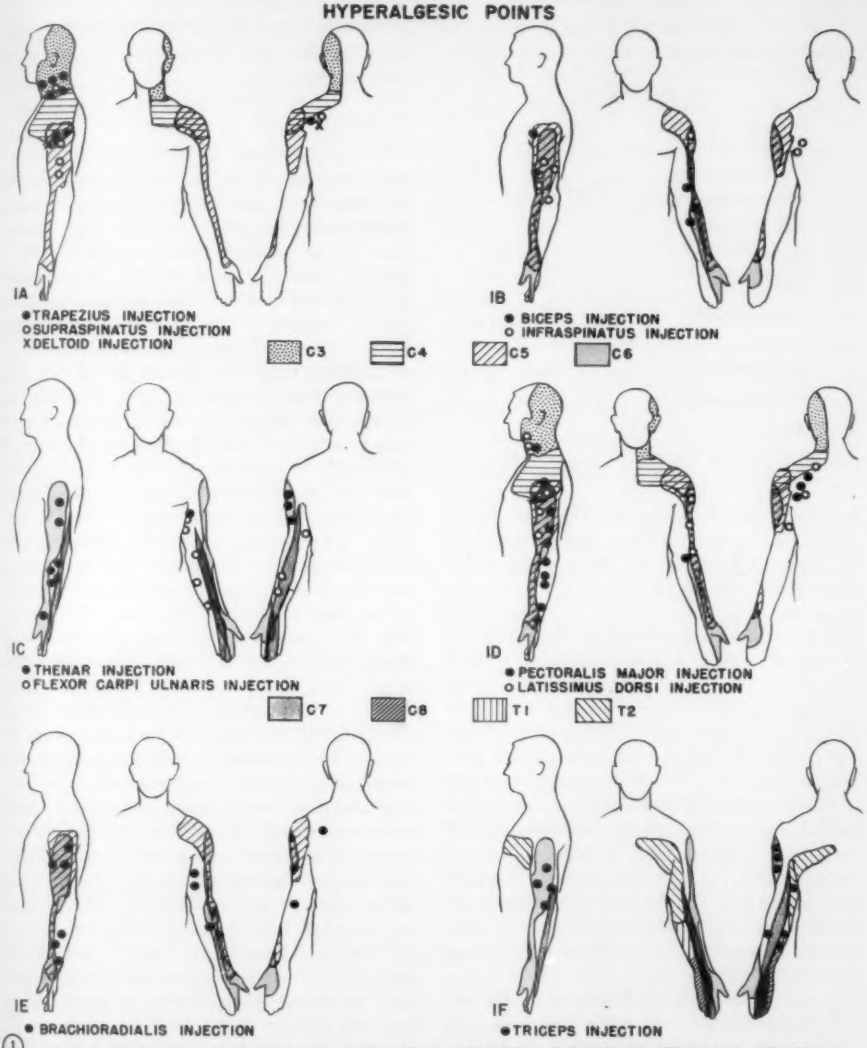


FIG. 1. *A.* The solid circles indicate the sites of hyperalgesia which followed the injection of hypertonic saline into the left trapezius muscle. The open circles indicate sites of hyperalgesia noted following injection of hypertonic saline into the left supraspinatus muscle. The *X* indicates site of hyperalgesia which followed injection of hypertonic saline into the left deltoid muscle.

B. The solid circles indicate sites of hyperalgesia which followed injection of hypertonic saline into the left biceps muscle. The open circles indicate sites of hyperalgesia which followed injection of hypertonic saline into the left infraspinatus muscle.

C. The solid circles indicate the sites of hyperalgesia which followed injection of hypertonic saline into the left thenar muscles. The blank circles indicate sites of hyperalgesia which followed injection of hypertonic saline into the left flexor carpi ulnaris muscle.

D. The solid circles indicate sites of hyperalgesia which followed the injection of hypertonic saline into the left pectoralis major muscle. The blank circles indicate the sites of hyperalgesia which followed injection of hypertonic saline into the left latissimus dorsi muscle.

E. The solid circles indicate the site of hyperalgesia into the left brachioradialis muscle.

F. The solid circles indicate the sites of hyperalgesia which followed injection of hypertonic saline into the left triceps muscle.

(The cutaneous sensory maps are derived from Foerster and Brock.)

TABLE 1

THE KNOWN MOTOR INNERVATION OF THE MUSCLES IN WHICH PAIN WAS INDUCED IS TABULATED (AFTER BRAIN)

Muscle	*Dermatome*
Trapezius	$C_{2,3,4}$
Supraspinatus	C_5
Infraspinatus	$C_{5,6}$
Deltoid	$C_{5,6}$
Biceps	$C_{5,6}$
Brachioradialis	$C_{5,6}$
Triceps	$C_{6,7,8}$
Latissimus dorsi	$C_{6,7,8}$
Pectoralis major	$C_{6,7,8}$
Thenar	$C_{8,7}$
Flexor carpi ulnaris	$C_{7,8}, D_1$

be seen from the diagrams that the hyperalgesic skin points conform approximately to the segments from which the muscles derive their motor innervation (table 1), with some exceptions. It is understood that the points stimulated were selected arbitrarily within the dermatome. Each square centimeter of each dermatome was not stimulated. Thus, when the trapezius was rendered painful, the hyperalgesic skin points were located in the third and fourth cervical dermatomes (figure 1A). Triceps pain resulted in hyperalgesic points localized within the sixth cervical dermatome and at the margins of the seventh cervical dermatome (figure 1F). A painful brachioradialis, however, resulted in some hyperalgesic points that were located within the fourth and seventh cervical dermatomes and not within those innervated by the fifth and sixth cervical nerves (figure 1E).

It was observed further that, after the initial diffuse muscle pain was experienced, it often became localized to a rather small area. This area of tenderness and pain was usually near the origin or insertion of the muscle and not at the injection point. After it disappeared, pain could be induced by using the muscle against resistance. On one occasion the triceps was made painful and then the seventh cervical dermatome was sprayed with ethyl chloride. This resulted in abolition of the muscle pain. Neither anesthetization of the contralateral seventh cervical dermatome nor spraying the other dermatomes in the same area had this effect.

DISCUSSION

The observations indicate that, under certain conditions, deep pain is accompanied by an alteration in cutaneous perception of pain. Furthermore, the site of altered pain perception can be more or less correlated with a specific painful muscle. If the observations are projected onto clinical entities, such as cervical radiculopathies and brachial plexus compression syndromes, they become useful in understanding the relationship of the distribution of deep pain, not only to cutaneous sensory phenomena but to the distribution of muscle weakness as well. Thus, in the case of a seventh cervical lesion, one might expect deep pain and weakness in a number of muscles innervated by the seventh cervical segment. Concurrently, cutaneous phenomena in the noncontiguous seventh cervical dermatome may be present, usually on the mid-dorsum of the hand and middle fingers. The relationship, for example, of pectoral pain to dysesthesias of the middle fingers and to weakness of the triceps and palmar abductor of the thumb, can, therefore, be understood more readily. This problem has been discussed by Brain[3] who, on clinical grounds, suggested that deep and superficial symptoms and signs have a relationship based upon a unitary spinal nerve innervation. We believe our observations support this thesis. Ever since Sturge[4] described the referred pain and dysesthesias of angina pectoris, the problem of referred pain has attracted a great deal of attention. Lewis and Kellgren[5] and Hardy, Goodell, and Wolff[6] produced cutaneous hyperalgesia experimentally by noxious stimulation of deep structures. Referred pain in deep structures induced by chemical and mechanical irritation was studied by Kellgren[7] and Inman and Saunders.[8] Although the latter authors did not include the investigation of cutaneous hyperalgesia in their study, they separated the superficial and deep segments, referring to the latter as "sclerotomes." They implied that the lack of anatomic continuity in depth between deep and superficial structures indicated that they are unrelated, in contrast to Brain's hypothesis of uni-

tary spinal nerve innervation. Attempts to explain the phenomenon of referred pain have been speculative. Sturge[4] postulated that cutaneous dysesthesias in angina pectoris were caused by "extension of commotion from one small patch of gray nerve substance to other parts associated with it." This explanation anticipated what is now described as "spread of central excitation" within a spinal segment and to other segments. Sinclair, Weddell, and Feindel[9] suggested an anatomic basis for areas of referred pain through the branched axon. Each axon is said to divide into a superficial and deep branch, so that pain impulses which travel over one branch may be "misinterpreted" in consciousness as having traveled over the other, and thus be referred to the region supplied by the other branch. The branched axon could also provide a pathway over which antidromic impulses may pass to cause liberation of a noxious metabolite,[10] with or without intermediate vasospasm.[11] This metabolite would then stimulate pain receptors. Sinclair, Weddell, and Feindel,[9] however, subscribe only to the concept of "central misinterpretation" in conjunction with the branched axon theory to explain the phenomenon of referred pain. Our findings can be interpreted on this basis.

Relief of deep pain by means of local cutaneous anesthesia has had an accepted place in therapy since Weiss and Davis[12] reported on the subject. They concluded that deep pain could be reduced or eliminated by anesthetization of skin areas "associated" with the deep pain areas. Because the anesthetized skin is not in itself a source of pain impulses, the question of the enhancement of pain by "normal" or subliminal impulses is raised. This problem has been treated by Cohen[13] and by Bremer.[14] The latter author concluded that "normal" impulses entering a spinal cord segment, into which noxious impulses are also streaming from a pain site, may play a role in intensifying pain. Our observation that deep pain was abolished by anesthetizing a "metamerically related" skin area supports this concept.

Trigger zones may be defined as localized areas in muscle or fascia which, when stimulated, initiate pain in neighboring or distal structures. Travell[15] considered them to be primary pain sites, thus implying that they are not in themselves sites of referred pain. It has been the observation of Kellgren,[7] Inman and Saunders,[8] and the present authors that induced deep pain often becomes localized to a circumscribed area which may be at the muscle attachment and/or near joints. Also, clinical experience has shown that, when radiculopathy is present, the muscles innervated by that particular segment may be tender in similar circumscribed areas. Therefore, we believe that so-called trigger areas themselves are often sites of referred pain of radicular origin and not necessarily primary pain sites.

SUMMARY AND CONCLUSION

1. Muscle pain was induced by injection of hypertonic saline solution, following which various skin areas were tested for pain perception by means of the Hardy-Wolff-Goodell thermal stimulator.

2. Discrete points of skin hyperalgesia were found which, with some exceptions, conformed approximately to the known segmental innervation of the painful muscles.

3. These observations indicate that cutaneous hyperalgesia, induced after a noxious agent is introduced into a muscle, occurs at a fairly predictable site, which is determined by the segmental innervation of the muscle.

4. The experimental observations clarify certain clinical observations regarding the distribution and relationship of deep and superficial sensory phenomena in radiculopathies.

5. Cutaneous anesthesia in the seventh cervical dermatome abolished pain and tenderness in the triceps muscle, thus offering support for the thesis that relief of deep pain by cutaneous anesthesia is based upon a segmental relationship of deep and superficial structures.

6. Following muscle injection with hypertonic saline, the pain soon became localized to a discrete area, usually near the attachment of the muscle. This observation is discussed in connection with so-called trigger zones, and the opinion is offered that trigger zones are often sites of referred pain and not primary pain sites.

REFERENCES

1. Foerster, O.: Dermatomes in man. Brain 56:1, 1933.
2. Brock, S.: Basis of Clinical Neurology, ed. 3. Williams and Wilkins Co., Baltimore, 1953, p. 72.
3. Brain, W. R.: Brachial neuralgia. Lancet 1: 393, 1948.
4. Sturge, W. A.: The phenomenon of angina pectoris and its bearing on the theory of counter-irritation. Brain 5:492, 1883.
5. Lewis, T., and Kellgren, J. H.: Observations relating to referred pain, visceromotor reflexes and other associated phenomena. Clin. Sc. 4:47, 1939-42.
6. Hardy, J. D., Goodell, H., and Wolff, H. G.: Studies of pain: Observations on the hyperalgesia associated with referred pain. Am. J. Physiol. 133:316, 1941.
7. Kellgren, J. H.: On the distribution of pain arising from deep somatic structures, with charts of segmental pain areas. Clin. Sc. 4:35, 1939-42.
8. Inman, V. T., and Saunders, J. B.: Referred pain from skeletal structures. J. Nerv. & Ment. Dis. 99:660, 1944.
9. Sinclair, D. C., Weddell, G., and Feindel, W. H.: Referred pain and associated phenomena. Brain 71:184, 1948.
10. Davis, L., and Pollock, L. J.: The role of the sympathetic nervous system in the production of pain in the head. Arch. Neurol. & Psychiat. 27:232, 1932.
11. Penfield, W.: The neurological mechanism of angina pectoris and its relation to surgical therapy. Am. J. M. Sc. 170:864, 1925.
12. Weiss, S., and Davis, D.: The significance of the afferent impulses from the skin in the mechanism of visceral pain. Skin infiltration as a useful therapeutic measure. Am. J. M. Sc. 176:517, 1928.
13. Cohen, H.: Visceral pain. Lancet 2:933, 1947.
14. Bremer, F.: Anatomy and physiology of pain. Acta Neurol. et psychiat. belg. 54:771, 1954.
15. Travell, J.: Pain mechanism in connective tissues. Tr. 2nd Conference, N. Y. Josiah Macy, Jr. Foundation, 1951, p. 86.
16. Kellgren, J. H.: Observations on referred pain arising from muscle. Clin. Sc. 3:175, 1937-38.

■ Instead of being merely a nerve centre—the special centre of Marshall Hall's excito-motor system of nerves—there is no reason to believe (as Dr. Brown-Séquard has so clearly shown), that the gray substance of the spinal cord is an important conductor of sensory and motor impressions. Paralysis without loss of sensation on the same side of the body, loss of sensation without paralysis on the other side of the body, are the strange results of cutting across one lateral half of the gray substance of the spinal cord: anaesthesia on both sides of the body, paralysis on neither side, are the equally strange results of making a vertical section midway between the two lateral halves: these are the two great facts which, when properly interpreted, furnish the reasons for believing, not only that there are sensorial and volitional conductors in the gray substance of the cord, but also that these two forms of conductors follow a different and definite course.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Cerebral hemispheric tumors and extrapyramidal signs and symptoms

Richard L. Roth, M.D.* and Jose Bebin, M.D., Ph.D.**

Tumors of the cerebral hemispheres, particularly neoplasms involving the basal ganglia, are usually not considered a cause of extrapyramidal symptoms and signs. In the literature one can find varied opinions, some of them conflicting. Mingazzini[1] and others have claimed to have established and confirmed a definite lenticular syndrome based on cases of brain tumors of the corpus striatum. Wilson[2] considered invasion of the basal ganglia by a tumor asymptomatic, but thought that focal neurologic signs appeared when the process extended into the internal capsule. With the exception of Ody[3] and of Sciarra and Sprofkin,[4] the majority of publications on this subject are reports of isolated cases limiting any definite conclusion. The purpose of this paper is to present an analytic study of a series of similar cases occurring in a larger number of hemispheric tumors involving the basal ganglia particularly. The clinical and anatomic findings are compared and discussed with other similar cases in the literature.

CASE MATERIAL

Approximately 400 histories and autopsies of patients with brain tumors were studied at the University of Michigan Hospital. Preferentially, cases in which definite localization of the tumor was verified by postmortem examination were selected, because the extent of a lesion often remains obscure from the operative point of view alone. Because no particular histologic type of tumor arises from the basal ganglia, for the purpose of this study one may include primary as well as metastatic tumors which affected and destroyed this region of the brain. Only cases with verified major or complete destruction of the basal ganglia and without extensive destruction of the surrounding structures, especially the internal capsule, were examined. Thirty-four cases were found, seven of which showed findings consistent with involvement of the basal ganglia. The findings were judged on the basis of the generally accepted opinion that disease of the basal ganglia manifests itself by one or more of the following clinical signs and symptoms: 1) hyperkinesia exemplified as involuntary movements such as choreic, athetoid, or ballistic; 2) akinesia exemplified by poverty of movements, with associated muscular rigidity and loss of associated movements; and 3) tremor, resting or intentional.

REVIEW OF THE LITERATURE

In 1864 Virchow[5] and Leyden[6] each published one case of unilateral paralysis agitans associated with tumor of the opposite optic thalamus. Parker[7] in 1923 reported three cases of brain tumor simulating epidemic encephalitis. One of his cases was a 12 year old boy who had weakness of the left side of the face and developed mask-like facies, walked slowly, and drooled saliva. In addition, he showed bilateral choreoathetoid movements and bilateral Babinski signs. At autopsy a diffuse infiltrating glioma involving both thalami and the right lenticular nucleus was found. Hunt and Lisa[8] described a patient 29 years of age with mask-like facies, tremor, and slowed gait which developed in the course of a brief illness characterized by severe headache and lethargy. The autopsy revealed a meningeal fibroma on the right frontal lobe, compressing the basal ganglia to half of their normal size. Moersch[9] reported a case of a man 28 years of age with parkinsonian facies and gait and tremor of the left upper extremity resulting

From the department of neurology and psychiatry, Henry Ford Hospital, Detroit, and the departments of neurology and neuropathology, University Hospital, Ann Arbor, Michigan.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 25, 1957.

*Present address: 215 Medical Arts Building, Louisville 10, Kentucky.

**Present address: Henry Ford Hospital, Detroit, Michigan.

from a parasagittal meningioma. These symptoms disappeared after removal of the tumor. Van Bogaert[10] discussed thalamic and parkinsonian types of infundibular tumors and described a case of a 46 year old woman who had a four-year history of seizures and diminishing vision for one year and exhibited retropulsion, slowness of movements, and amimia due to pressure on the basal ganglia by a basal tumor. Brzezicki[11] reported two cases of neoplasms of the basal ganglia. In one, parkinsonian symptoms involving the face and arm were present and were assumed to be due to a spongioblastoma involving the head and anterior part of the body of the caudate nucleus, the anterior half of the putamen, and the anterior limb of the internal capsule. In the second case, the patient had a right hemiparesis complicated by generalized rigidity and amimia. Tremor was absent, however. Autopsy revealed a deep intracerebral tumor which destroyed the left thalamus, putamen, globus pallidus, and internal capsule and extended into the brainstem. Ody[2] studied a series of 25 brain tumors arising in or involving the basal ganglia. He gave detailed accounts of seven cases, five of which exhibited specific symptoms of a lesion of the basal ganglia. In his study he indicated that most of the symptoms, which apparently characterized involvement of this region by tumors, are nothing but manifestations of partial decerebration and that tumors of the basal ganglia do not present any specific signs or symptoms. Alexander[12] published two cases of brain tumors in which hyperkinetic amyotatic phenomena were present. The first case was a 24 year old woman with right hemiparesia and tremor, severe choreoathetosis, and rigidity. An astroblastoma destroying both thalami and striopallidum was found at autopsy. The internal capsule was compressed, but not invaded by the tumor. The second case was a 42 year old woman with generalized spasticity without paralysis, choreiform hyperkinesis involving the left arm and leg, and bilateral Babinski signs. At autopsy a fibrillar astrocytoma destroying the head and anterior part of the body of the caudate nucleus was encountered. Grant[13] reported a case of brain tumor with parkinsonian manifestations in a 28 year old man with a history of widespread paresthesias followed by visual, auditory, and olfactory hallucinations. He had a constant tremor of the right foot. The autopsy revealed a large astrocytoma arising in the left temporal lobe. Hippocampal herniation and edema compressed the left lenticular nucleus and adjacent cerebral peduncle. Urechia, Dragomir, and Usinievici[14] described a case of a 14 year old boy with progressive spasticity and contracture of the hand, followed by torsion spasm of that side of the body. At autopsy a glioblastoma in the contralateral hemisphere compressing the putamen, caudate nucleus, and part of the globus pallidus was found. Mettler, Davidoff, and Grimes[15] described a patient who, at age six years, presented resting tremor of the right upper and lower extremities. Diagnosed as having an inoperable tumor of the floor of the third ventricle, she was treated with radiation therapy and did well for the following seven years. The patient then developed a right hemiparesis, but continued with constant motion of the right upper extremity. Autopsy showed a massive polar spongioblastoma in the diencephalon and mesencephalon, with compression and infiltration of the left thalamus as well as the midbrain. Schlesinger,[16] in a study of 20 gliomas involving the corpus callosum, reported basal ganglia signs in seven cases (35 per cent). A parkinson-like tremor in one upper extremity was present in cases 2 and 10, retropulsion in case 11, slight generalized rigidity in case 2, a continuous coarse tremor in the trunk and proximal part of the lower limbs in case 4, akinesia in case 13, attacks of rhythmic opening and closing of the jaw in case 13, and a generalized tremor in case 17. The relevant finding at autopsy was unilateral destruction of the head of the caudate nucleus in case 4. Otherwise, the findings shed no light on the clinical picture, and whether tumefaction of the corpus callosum either compressed the basal ganglia or gave rise to local edema could not be stated. Sciarra and Sprofkin[4] reported 12 cases of brain tumors with manifestations of extrapyramidal disease. Ten cases (2 per cent) were found among 474 patients with brain tumors admitted to the Neurological Institute of New York in a two-year period. Seven patients had evidence of pyramidal tract involvement. A rhythmic alternating tremor was the most com-

mon extrapyramidal sign. Other extrapyramidal manifestations included athetosis, torsion spasm, rigidity, and bradykinesia. Their 12 cases represented varied types of tumors: five glioblastomas, two astrocytomas, one fibroma, one metastatic carcinoma, and three unclassified tumors. The extent of involvement of the basal ganglia and other structures by the neoplasm was only verified at autopsy in four of the cases (cases 3, 5, 7, and 8). In case 3, a 21 year old woman with tremor of the left arm for nine years, a mixed glioma of the right thalamus extending into the lenticular nucleus and island was found. Case 5 was a 29 year old woman with choreoathetoid movements of the right upper extremity for three years. At autopsy a large firm encapsulated fibroma nested in the left choroidal fissure and compression of the cerebral peduncle and basal ganglia was encountered. Case 7 was a 15 year old girl with progressive contracture of the left hand for one month and involuntary movements of the left great toe for two weeks. The autopsy showed a glioblastoma of the left frontal lobe involving the basal ganglia and thalamus. Case 8 was a 63 year old man with rhythmic tremor of both hands for two weeks. The autopsy revealed an infiltrating glioblastoma of the corpus callosum invading the right thalamus.

REPORT OF CASES

Case 1. A 45 year old white female. Increased intracranial pressure syndrome for eight months. Ataxia and lethargy, papilledema, left Babinski. Glioblastoma multiform of septum pellucidum extending to right caudate nucleus and right globus pallidus.

Case 2. A 45 year old white female. Headaches and generalized convulsions, right hemiparesis. Glioblastoma multiform destroying right basal ganglia and island region.

Case 3. A 40 year old white male. Numbness of the right side of the body for four months, mental confusion, right hemiparesis. Glioblastoma multiform of left hemisphere destroying basal ganglia and invading thalamus and internal capsule.

Case 4. A 77 year old white male. Frontal headaches, comatose, increased tonus in left extremities, papilledema. Glioblastoma multiform destroying the right basal ganglia and invading the internal capsule.

Case 5. A 22 year old white female. Headaches, numbness on the right, obesity, bilateral ptosis, weakness of right arm, right hypesthesia, and right Babinski. Spongioblastoma infiltrating the basal ganglia, thalamus, and brainstem.

Case 6. Headache and dizziness for one month, papilledema, left homonymous hemianopsia, lack of associative movements, left hypesthesia, calcification on right basal ganglia. Oligodendroglioma of right basal ganglia region.

The patient was a 43 year old white male who entered the University Hospital with the chief complaint of headache and dizziness of one month duration. He felt unsteady on his feet. He admitted to periods of confusion during which "objects" did not seem "normal." There were no other complaints. Examination revealed a healthy appearing white male who was oriented, but seemed to have some recent loss of memory. The right pupil was larger than the left and reacted slowly to light. There was limitation of lateral gaze to the right. A left homonymous hemianopsia was present. There was papilledema. A very mild left hemiparesis was noted and there was lack of associated motor movements. A bilateral intention tremor and left-sided hypesthesia, including vibratory sense and position sense, were present. The deep tendon reflexes were hyperactive on the left.

Routine laboratory findings were normal, including spinal fluid studies. Ventriculogram showed moderate dilatation of the lateral ventricles with displacement of both frontal horns to the left and displacement of the third ventricle to the left. Calcification in the region of the basal ganglia on the right was noted. The patient was operated upon for partial removal of the tumor. The patient was discharged, and readmitted 17 months later with headache and vomiting. There was an increase in the left hemiparesis. A second operation for partial removal and decompression was performed. The patient was discharged and readmitted to another hospital two years later where he died. No gross description of the brain was available. The histologic diagnosis was an oligodendroglioma with areas of calcification. From the operative description it is thought that the basal ganglia on the right side were destroyed.

Case 7. A 23 year old white female. Headaches, ataxia, papilledema, and left hemiparesis. Tumor of right hemisphere involving the thalamus, caudate nucleus, and lentiform nucleus.

Case 8. A 37 year old white female. Headaches and personality change for several months, focal seizures, unconsciousness, papilledema, and right Babinski. Right frontal lobe oligodendroglioma involving caudate nucleus, putamen, and genu of corpus callosum.

Case 9. A 55 year old white female. Headaches and left hemiparesis, papilledema. Glioma of right temporoparietal region invading lentiform nucleus and cerebral peduncle.

Case 10. Mental changes, fever, coma, bilateral tremor of hands and arms. Metastatic hypernephroma to temporal lobe and lentiform nucleus.

The patient was a 72 year old white male who

was hospitalized at the Michigan Asylum for the Insane because of mental incompetence. He had been well and there was no past history of disease. Rather suddenly he became markedly ill with fever and soon lapsed into coma. Examination revealed an elderly male. At the junction of the middle and upper third of the right thigh, there was a marked enlargement which was hard. There was a coarse tremor of the hands and arms bilaterally. The left pupil was dilated and fixed. The patient soon expired.

At autopsy the mass in the right lower extremity was found to be an osteosarcoma. There was a hypernephroma of the kidney. The brain weighed 1,390 gm. and the convolutions were flattened. Some cortical atrophy was present. Sections revealed a dark hemorrhagic tumor in the white matter beneath the first and second temporal convolutions pressing on the basal ganglia. A small cyst was seen in the lenticular nucleus. Histologically this was a hypernephroma.

Case 11. Mental changes, ataxia, and tremor. Malignant glioma of right basal ganglia involving corpus callosum.

The patient was a 43 year old white male who entered the Pontiac State Hospital because of increasingly severe mental changes. The impression was general paresis. He had an episode of headache, chills, and fever, with ensuing sleepy spells. Some ataxia of fine movements and tremor was noted. His condition deteriorated progressively and he expired.

At autopsy the brain weighed 1,540 gm. Cut sections showed a large tumor on the right involving and destroying the basal ganglia, with some invasion of the internal capsule, frontal radiations, and corpus callosum. There was some softening of the left caudate nucleus. The histologic diagnosis was a malignant glioma.

Case 12. A 54 year old white female. Mental changes, right hemiplegia with aphasia. Glioma of left temporal lobe infiltrating the lentiform nucleus, internal capsule, and thalamus.

Case 13. Convulsions, memory loss, fixed pupils, hyperreflexia, left facial weakness, optic atrophy, and tremor of both hands. Astrocytoma of right basal ganglia and thalamus.

The patient was a 44 year old white male who was admitted to the hospital because of increasing memory impairment and onset of convulsions. Examination revealed fixed pupils, increased deep tendon reflexes, ankle clonus on the left, left facial weakness, and tremor of the hands. There was moderate optic atrophy. Spinal fluid was normal, except for a positive Pandy. At autopsy the meninges were thickened and cloudy about the optic chiasm. Cut sections showed a tumor mass involving the right thalamus and the basal ganglia. The histologic diagnosis was an astrocytoma.

Case 14. A 14 year old white female. Focal seizures involving left arm, lethargy and papilledema, ataxia, jerking and increased tonus on left arm, bilateral Babinski. Astrocytoma of the region of the third ventricle destroying the right basal ganglia, thalamus, and subthalamus.

Case 15. A 52 year old white male. Severe headaches for several months, weakness of left side of the body, convulsions, and coma. Necrotic astrocytoma of the right basal ganglia.

Case 16. A 42 year old white female. Inability to see to the left, headaches, left homonymous hemianopsia, left hemiparesis, and left hemihypesthesia with Babinski. Large astrocytoma of right hemisphere involving basal ganglia, thalamus, internal capsule, and midbrain.

Case 17. A 53 year old white male. Forgetfulness and confusion for several months, right hemiparesis, dysarthria. Glioblastoma multiform, left hemisphere involving anterior part of basal ganglia and corpus callosum.

Case 18. A 29 year old white male. Severe headache and blurred vision with diplopia, confusion, papilledema, and questionable right homonymous hemianopsia. Glioblastoma of the third ventricle extending into left thalamus, basal ganglia, and brainstem.

Case 19. A 33 year old white female. Generalized convulsions, numbness, left side of the body, disoriented and drowsy, left hemiparesis, hemihypesthesia, and left homonymous hemianopsia, third nerve paresis. Glioblastoma of right hemisphere involving the basal ganglia and thalamus.

Case 20. A 29 year old white male. Headaches, dizziness, inability to see to the left, bilateral sixth nerve paresis, slow movements of the left arm, left homonymous hemianopsia. Astrocytoma left frontotemporooccipital extending to basal ganglia and midbrain.

Case 21. A 15 year old white female. Headaches, difficulty in speech, paresthesias of right hand and foot, ataxia, and mild right hemiparesis. Glioblastoma of left hemisphere infiltrating basal ganglia, thalamus, and internal capsule.

Case 22. A 51 year old white male. Headache and dizziness following head injury, left homonymous hemianopsia, left facial weakness, and sixth nerve paresis. Glioblastoma of the right hemisphere involving basal ganglia.

Case 23. A 58 year old white male. Increasing difficulty with vision, right homonymous hemianopsia, mild expressive aphasia. Large glioma occupying the left parietal lobe, chiasm, temporal lobe, and basal ganglia on left.

Case 24. Pain in right eye and head, constant tremor of the jaw, hypesthesia of right side of the face. Glioblastoma right parietotemporal extending to basal ganglia and thalamus.

The patient was a 55 year old white female who entered the University Hospital with a vague history of right eye and head pain of long duration.

Examination revealed a patient who retracted the right side of the face and kept the right eye closed. She had a constant tremor of the jaw, especially on the right side. The right side of her face was more sensitive to touch and pin prick. The rest of the examination was normal. Ven-

triculogram revealed moderate dilatation of the lateral ventricles and the third ventricle. There was a pronounced shift of the system to the left. The patient underwent a craniotomy, with partial removal of the tumor.

At autopsy the brain weighed 1,370 gm. Sections revealed tumor tissue in the right temporoparietal region extending into and involving the basal ganglia and thalamus. The histologic diagnosis was glioblastoma multiform.

Case 25. A 51 year old white male. Severe headaches, fatigue, weakness of left lower extremity, questionable left homonymous hemianopsia, and hypesthesia. Glioblastoma of right hemisphere destroying basal ganglia and involving internal capsule.

Case 26. Projectile vomiting, ataxia, internal strabismus, generalized tremor more on right. Malignant glioma of left temporoparietal region invading basal ganglia and corpus callosum.

The patient was a three year old white female who entered the University Hospital because of projectile vomiting. A few weeks before admission the mother noted that the right eye turned inward. The patient refused to walk and she appeared quite unsteady. The mother described tremor of the entire body, especially marked in the right arm.

Examination revealed an irritable child with apparent paresis of both external recti muscles. The right arm was ataxic and had almost constant tremulous movements.

At autopsy the brain weighed 1,300 gm. There was a large tumor in the left parietotemporal region involving the white matter, basal ganglia, and corpus callosum. The left cerebral peduncle was invaded. The histologic diagnosis was an undifferentiated glioma.

Case 27. Vomiting, headache, staggering gait, hyperreflexia, loss of position sense on left arm and leg with choreoathetoid movements. Malignant glioma right hemisphere destroying basal ganglia.

The patient was a 27 year old white male who entered the University Hospital because of numbness of the left side of his body about six months before. Two months prior to admission he noted staggering, with a tendency to fall to the left. Onset of headache and vomiting was about one week prior to admission.

Examination revealed bilateral papilledema. The left upper extremity was hypotonic and weak, with a tendency to deviate outward when outstretched. The left hand and fingers assumed bizarre posture with athetotic movements. Coordination testing showed marked ataxia in the left upper extremity. The left lower extremity also was somewhat weak and hypotonic and displayed considerable ataxia on testing. Sensory examination showed severe loss of position and motion sense on the left side. Touch and pain sensation were preserved. The deep tendon reflexes were hyperactive on the left side and an extensor plantar response was obtained on the left. The patient underwent a craniotomy with partial removal of tumor. Postoperative progress was good. Eight months later he was re-admitted because of seizures, treated with radiation, and again discharged. Four months later he developed signs of increased pressure. He was reoperated upon and died.

At autopsy there was evidence of increased pressure. Tumor tissue was present in the right hemisphere, destroying the basal ganglia and invading the internal capsule and the corpus callosum. The histologic diagnosis was undifferentiated glioma.

Case 28. A 42 year old white female. Progressive weakness of right hand, mild right hemiparesis, and right homonymous hemianopsia. Glioblastoma multiform destroying left globus pallidus, amygdaloid nucleus, pulvinar and cerebral peduncle.

Case 29. A 53 year old white male. Progressive right hemiparesis, headaches, vomiting, questionable right hemihypesthesia. Glioblastoma left parietal region destroying basal ganglia, internal capsule, and thalamus.

Case 30. A 47 year old white male. Progressive weakness of left arm and leg, dimming of vision, left hemiplegia, hypesthesia on the left side of face. Large glioma destroying right basal ganglia, internal capsule, and thalamus.

Case 31. A 53 year old white male. Headaches, memory loss, disorientation, confusion. Right fron-

TABLE 1

CLINICAL MANIFESTATIONS OF 34 CASES OF HEMISPHERIC TUMORS INVOLVING THE BASAL GANGLIA

		Total
Increased intracranial pressure	Cases: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 14, 15, 18, 19, 20, 21, 22, 23, 25, 26, 27, 29, 30, 31, 32, 33, 34	28
Hemiparesis and/or pyramidal tract signs	Cases: 1, 2, 3, 4, 5, 7, 8, 9, 12, 14, 15, 16, 17, 19, 20, 21, 22, 25, 28, 29, 30, 32, 33, 34	24
Convulsions	Cases: 2, 8, 11, 12, 13, 14, 15, 19, 28, 29, 32, 33, 34	13
Sensory changes	Cases: 3, 5, 6, 16, 19, 21, 22, 24, 25, 27, 29	11
Mental changes	Cases: 6, 8, 10, 11, 12, 17, 31, 33	8
Extrapyramidal signs or symptoms	Cases: 6, 10, 11, 13, 24, 26, 27	7
Aphasia or dysarthria	Cases: 12, 17, 23	3

tal glioblastoma invading basal ganglia, thalamus, and corpus callosum.

Case 32. A 32 year old white female. Changes in behavior, "wandering spells," generalized seizures, left hemiparesis, chronic pulmonary tuberculosis. Tuberculoma of the basal ganglia region, including the thalamus and extending into brainstem.

Case 33. A 58 year old white male. Increasing memory loss, headaches, occasional diplopia, left hemiparesis. Oligodendroglioma of right frontal lobe with invasion of caudate nucleus, ventricular nucleus, and internal capsule.

Case 34. A 12 year old white female. Severe headache and vomiting, double vision, generalized seizures, questionable bilateral Babinski. Large malignant glioma infiltrating the left thalamus and basal ganglia region.

COMMENTS

Of the 34 cases of hemispheric tumors involving the basal ganglia reviewed, only seven cases showed clinical symptomatology consistent with involvement of these ganglia. This represents approximately 20 per cent of this selected group of cases. The predominant clinical manifestations (table 1) were increased intracranial pressure, hemiparesis and pyramidal tract signs, convulsions, sensory deficit, mental changes, extrapyramidal signs and symptoms, and aphasia. The absence of basal ganglia manifestations in the majority of cases can be explained because of the tumor involvement and destruction of extensive areas of the brain, including the internal capsule. It is a well known fact that involvement of the motor pathways by the pathologic process abolishes some of the manifestations of parkinsonism and particularly tremor and other hyperkinetic manifestations of basal ganglia disease. Examination of table 1 shows that cases 6, 10, 11, 13, 24, and 26 with extrapyramidal manifestations had no symptoms or signs referable to involvement of the internal capsule and no damage of the capsule was found at autopsy. Absence of secondary associated movements, tremor of the extremities, tremor of the jaw, dystonia, and choreoathetoid movements were the extrapyramidal manifestations present (table 2). Of these, tremor was the most frequent and occurred in five cases. Absence of associated motor movements was noted in one case, and tremor of the jaw and blepharospasm were present in one case. Dystonia and choreoathetoid movements of the left extremities were present in one case. In six of these cases (cases 16, 11, 13, 24, 26, and 27) at operation and autopsy, a primary tumor of the brain was found. There were four malignant gliomas, one astrocytoma, and one oligodendroglioma. In case 10 a metastatic hypernephroma was found. In the study of the material it was difficult to disclose the exact site of origin of the tumor. Whether they arise in the basal ganglia and subsequently invade

TABLE 2

Case No.	*Age*	*Sex*	*Admission Symptoms*	*Signs and Symptoms*	*Extrapyramidal Manifestations*	*Pathology*
6	43	M	Headache, dizziness	Hyperactive reflex, left hypesthesia, calcification of right B.G.	Lack assoc. mov., bilateral tremor	Oligodendroglioma of right B.G. region
10	72	M	Mental changes	Fever and coma	Bilateral tremor of hands and arm	Metastatic hypernephroma to temp. lobe and B.G. (lentiforme nucleus)
11	43	M	Mental changes	Ataxia	Bilateral tremor	Malignant glioma of right basal ganglia invading c. callosum
13	44	M	Convulsions, memory loss	Fixed pupils, hyperreflexia left facial weakness, optic atrophy	Tremor of both hands	Astrocytoma of right basal ganglia and thalamus
24	33	F	Pain on right eye and head	Hypesthesia right side of face	Constant tremor of jaw	Glioblastoma right parieto-temp. destroying B.G. and thalamus
26	3	F	Projectile vomiting	Internal strabismus, ataxia	Generalized tremor, more on right extr.	Malignant glioma left temporo-parietal invading B.G. c. callosum
27	27	M	Vomiting, headache, staggering gait	Hyperreflexia, loss of position sense on left	Distonia left arm and leg, choreoathetoid movements	Malignant glioma, right hemisphere destroying B.G. and invading c. callosum

the surrounding structures, or vice versa, cannot be established with certainty. In no case was the neoplasm strictly limited to the basal ganglion structures alone. In case 6 calcification of the basal ganglion region was found on roentgenography of the skull, and at operation an oligodendroglioma was found in that region. The patient presented bilateral tremor and loss of associated movements. In case 11 a malignant glioma involving the entire right basal ganglia invading the corpus callosum and the anterior limb of the internal capsule was found. This patient presented bilateral tremor. Case 13 also presented tremor and an astrocytoma involving the right basal ganglia and thalamus was encountered. Case 24, with tremor of the jaw, blepharospasm, and hyperesthesia of the right side of the face, had a large glioblastoma of the parietotemporal region destroying the basal ganglia and thalamus. Tremor predominant in the right extremities was present in case 26 which showed a malignant glioma of the left temporoparietal region including the basal ganglia and corpus callosum. In case 27 choreoathatoid movements of the left arm and dystonia of the left extremities were observed. The autopsy showed a malignant glioma destroying the right basal ganglia and extending into the corpus callosum.

In relation to location of the lesion responsible for parkinsonian syndrome in brain tumors, the most favored views are the involvement of frontal lobes or the basal ganglia. Numerous authors[9,13,17] have described parkinsonian syndromes following tumors in the frontal region. It is well accepted that frontal lesions may produce apathy, akinesia, amimia, and disturbances of equilibrium. These symptoms suggest parkinsonism, but do not strictly belong to this condition, and some of the cases of frontal lobe tumor published cannot be accepted as true examples of parkinsonism. Others, however, seem to fulfill the clinical requirements, that is, cogwheel rigidity, akinesia, resting tremor, and mask-like facies. Several hypotheses have been advanced to explain the presence of this syndrome in prefrontal neoplasma. Lesions compressing the basal ganglia may produce hypertonicity. Schuster[18] published two examples of this type. In some cases the lesions were bilateral and almost invariably invaded the corpus callosum.[16] In some cases of parkinsonian syndrome due to prefrontal tumor,[9] extirpation of the tumor was followed by disappearance of the symptoms. Compression of the basal ganglia as the cause for the symptomatology observed in such cases cannot be accepted in all instances. There are numerous cases in which the basal ganglia were compressed, invaded, and even destroyed by neoplasms without presenting typical symptomatology. One must search for the explanation for this difference in a more complex mechanism which may include, as already suggested by Wilson,[19] corticosubcortical mechanisms. The symptoms and signs do not result from direct or indirect compression of the basal ganglia above, but principally from the interruption of the connections between prefrontal cortex, areas 6 and 8, with the putamen and areas 6s and 8s with the caudate nucleus. These fibers—with or without relays in these nuclei—reach the globus pallidus. Connections from the temporal lobe and the island region passing through the sublenticular portion of the internal capsule reach the putamen and globus pallidus. From the basal ganglia the impulses are relayed along the lenticular fasciculus and the ansa lenticularis to the midbrain tegmentum. The prefrontal as well as the temporal fibers pass with or without synapse in the basal ganglia, into the homolateral tegmentum of the midbrain, where, among other systems, for example, the cerebellorubrothalamic fibers also end. "It is evident, that many fiber systems are interrelated in the tegmentum of the midbrain. Any impulse relayed forward from this area will be the result of an interplay among the discharges from a considerable range of central nervous system centers."[20] These circuits could then be disrupted in cortical lesions, either prefrontal or temporoparietal, as well as basal ganglia and tegmental lesions. The lesions, in final analysis, disturb the equilibrium between corticobasal ganglia influences and cerebellar discharges at midbrain level. The symptomatology observed is the result of this imbalance produced by the lesions.

In this series of 34 hemispheric tumors involving the basal ganglia, extrapyramidal manifestations were present in seven cases. No signs of pyramidal involvement were pres-

ent in these cases. In 27 cases in which pyramidal signs were also present, the internal capsule was included in the lesion. This indicates that the integrity of the pyramidal pathway is necessary for manifestation of the clinical symptomatology.

REFERENCES

1. Mingazzini, G.: Das Lisenkernsyndrome Klinische und anatomischpathologische Beobachtungen. Ztschr. Neurol. u. Psychiat. 8:85, 1912.
2. Wilson, S. A. K.: Neurology. Baltimore, William Wood and Company, 1940, Vol. 2.
3. Ody, F.: Tumors of the basal ganglia. Arch. Neurol. & Psychiat. 27:249, 1932.
4. Sciarra, D., and Sprofkin, B.: Symptoms and signs referable to the basal ganglia in brain tumors. Arch. Neurol. & Psychiat. 69:450, 1953.
5. Virchow, R.: Krankhafte Geschwiilste, Berlin, Hirschwald, 1864.
6. Leyden, E.: Fall von Paralysis Agitans des rechten Arms infalge von Entwicklung eines Sarcoms in linken Thalamus. Arch. Path. Anat. 29:202, 1864.
7. Parker, H. L.: Tumors of the brain simulating epidemic encephalitis and involving third ventricle, fourth ventricle, and basal ganglia. J. Nerv. & Ment. Dis. 58:1, 1923.
8. Hunt, E. L., and Lisa, J. R.: Frontal lobe tumor, a case simulating epidemic encephalitis with parkinsonian syndrome. J.A.M.A. 89:1674, 1927.
9. Moersch, F. P.: Tumors of the frontal lobe presenting a parkinsonian syndrome. Minnesota Med. 11:734, 1928.
10. Van Bogaert, L.: Thalamic and parkinsonian type of infundibular tumors, occurrence of glycoregulatory and so-called endrocrine disorders. Arch. Neurol. & Psychiat. 19:377, 1928.
11. Brzezicki, E.: Der Parkinsonismus symptomaticus. 5. Mitteilung: Zur Frage des Parkinsonismus bei der Kohlenoxydvergiftung. Arb. Neurol. Inst. Univ. Wien 32:148, 1930.
12. Alexander, L.: The fundamental types of histopathologic changes encountered in cases of athetosis and paralysis agitans. In Basal Ganglia, A.R.N.M.D. XXI. Baltimore, The Williams & Wilkins Company, 1942, pp. 464-468.
13. Grant, W. T.: Brain tumor with parkinsonian manifestations: Report of a case. Bull. Los Angeles Neurol. Soc. 8:139, 1943.
14. Urechia, C. I., Dragomir, and Usinievici, G.: Spasme de Torsion Unilateral cause par une Tumeur Cerebrale. Confinia neurol. 5:271, 1943.
15. Mettler, F. A., Davidoff, L. M., and Grimes, R.: Static tremor with hemiplegia. Report of a case; Development, progression for seven years and post-mortem histologic observation. Arch. Neurol. & Psychiat. 57:423, 1947.
16. Schlesinger, B.: Glioma involving splenium of corpus callosum. Neurology 1:419, 1951.
17. Bostroem, A.: Zur diagnose der Stirnhirntumoren. Deutsche Ztschr. Nervenh. 70:82, 1921.
18. Schuster, P.: Kann ein Stirnhirntumor das Bild der Paralyse agitans hervorrufen? Ztschr. Neurol. u. Psychiat. 77:1, 1922.
19. Wilson, S. A. K.: Modern Problems in Neurology. New York, William Wood & Company, 1929.
20. Crosby, E. C.: The role of the midbrain as a part of the discharge paths from higher centers. Proceedings of the First International Meeting of Neurobiologists. Groningen, 1955.

■ The generalisation is that *destruction* of a considerable part of either the cerebrum or cerebellum (especially if that destruction be effected slowly) can occur without the production of striking symptoms of any sort—"mental" or "physical." Now, mark that I say *destruction;* I do not use the vague expression "disease." If even a *small* tumour of the surface of the cerebrum leads to *instability* of neighbouring grey matter, then you may have very marked motor symptoms. You may then have motor symptoms of two opposite sorts. There is first convulsion—the direct result of the discharge of the unstable grey matter—and second there may be, as an indirect result of the discharge, paralysis of the parts "overworked" in that convulsion.

J. Hughlings Jackson in *Lectures on the Diagnosis of Tumours of the Brain,* published in 1872.

Progressive demyelinating leukoencephalopathy

Frederick J. Wohlwill, M.D. and Richmond S. Paine, M.D.

THE MAJOR TYPES of progressive demyelinating leukoencephalopathies are familiar to all neurologists. The mechanisms involved, however, remain much more obscure, perhaps because of the limited number of cases fully documented clinically and pathologically, and because of the numerous atypical forms and intertypes between different classifications. Thus, as Greenfield[1] has stated, "It remains important that all unusual cases of diffuse sclerosis should be fully reported."

Although identification of pathologic types can be only speculative during life, cases suspected of the diagnosis in the group under discussion are seen from time to time in every large children's clinic. It is only by assiduous attention and continual personal contact with families that proper follow-up information can be obtained, followed by the necessary pathologic examination. Although the children involved seldom die during their original hospital admission, we have found it possible to obtain for examination the brains of a number of infants who have died at home or in various institutions. Two such cases will now be reported.

SUMMARY OF CLINICAL DATA — CASE 1

A white, male infant was first seen at the age of five and a half months because of regression in interests and activities from the age of four and a half months. The baby was the product of a full term normal delivery following a normal pregnancy. Birth weight was 9 pounds and no resuscitation was required. The newborn period was entirely normal, and the baby was thought to be normal in every way until about the age of four months. He had had no illnesses or known trauma.

Family history. Both parents were in good health and of above average educational and economic background. There was no consanguinity. Detailed family history was obtainable as far back as the patient's grandparents and their siblings; it contained no instances of neurologic disease. The patient had three sisters, aged two, six, and nine and a brother aged eight years. All of them were well.

Present illness. At the age of four months the patient was able to roll over and had excellent head control. Shortly thereafter he began to regress, failed to hold up his head, and lost all interest in people and objects. It became uncertain whether he saw or heard. Seizures began at about the age of four months and were characterized by stiffening, rolling up of the eyes, assumption of the opisthotonic position, and loss of contact with the environment for perhaps half a minute. There was no twitching and no postictal sequelae were observed. At least several such episodes occurred daily. In the two weeks preceding the first examination, the baby refused to take solid food and drank liquids with some difficulty.

Physical examination. The patient was a well nourished baby of five and a half months who tended to lie in opisthotonus but without rigidity, except during the seizures described above. The head was 43.5 cm. in circumference. There were aimless movements of the eyes, which frequently rolled up under the upper lids. There was no evidence that the baby saw or heard. The pupils reacted somewhat sluggishly to light unless the illumination was very strong. The eyegrounds were normal. Muscle tone was normal, and there were constant aimless movements which were not especially vigorous. The reflexes were lively but not exaggerated, with the exception of the knee jerks. The Babinski sign was more strongly positive bilaterally than would be expected for the patient's age. There was no ankle clonus. Very strong tonic neck reflexes were obtained in both directions. Otherwise the examination was negative.

Routine blood and urine studies were negative, including examination of the urine for phenylpyruvic acid. Roentgenograms of the skull were normal, as was an electroencephalogram. Lumbar puncture produced normal spinal fluid under normal pressure, except for a total protein of 49 mg. per 100 ml. Subdural taps were negative. A pneumoencephalogram was normal, except for a rather large amount of subarachnoid air.

Cortisone was given in doses of 100 mg. daily for 24 days and then gradually withdrawn. There was no change in the child's condition during this period.

From the department of neuropathology and the Warren Anatomical Museum, Harvard Medical School, the department of medicine, Children's Medical Center, and the department of pediatrics, Harvard Medical School, Boston, Massachusetts.

Supported in part by grants-in-aid from the United Cerebral Palsy Association.

The clinical diagnosis was a progressive leukoencephalopathy and the prognosis was believed to be hopeless. The child was transferred to a state institution for terminal care. While there, he had numerous respiratory infections and died of pneumonia at the age of nine months.

Autopsy. A few foci of bronchopneumonia were seen in the lungs.

The heart weighed 79.5 gm. (normal 37 gm.). The walls of both ventricles were thickened: right ventricle, 3 to 5 mm.; left ventricle, 10 to 11 mm. The myocardium showed some indistinct grayish-yellow mottling. There was a fibroelastosis limited to the endocardium of the left atrium. Microscopically the myocardium was essentially normal. A definite cause of the hypertrophy of the heart could not be verified.

In the remaining body organs no remarkable macroscopic or microscopic changes were noted.

The brain weighed 780 gm. (normal 750 gm.). Externally no pathologic changes were noted. After fixation the whole white matter of the hemispheres showed, on the cut surface, a peculiar type of softening in the form of white, web-like depressed areas. There were no hemorrhages and no discoloration. The softening involved all lobes, but the subcortical arcuate fibers seemed to be spared. The process extended into the lateral parts of the corpus callosum. Bilaterally, at about the level of the locus caeruleus, there were crescent-shaped dark brown areas 0.1 to 0.2 cm. in size. The substantia nigra was unusually prominent. No areas of softening or discoloration were grossly evident in the basal ganglia, brainstem, or internal capsule. The ventricles were not dilated.

Microscopic findings. Loyez-stained sections of the hemispheres cut in frontal plane showed to naked-eye examination complete demyelination of the centrum semiovale and the subcortical white matter, except for most of the arcuate fibers which appeared as a black line between the cortex and the white matter. In some gyri, however, this black ribbon was absent so that the demyelinated white matter was immediately adjacent to the cortex (figure 1). The corpus callosum stained in a somewhat spotty way, but was normally myelinated in general. The internal capsule was partially demyelinated.

Microscopically three types of changes could be distinguished. The medial part of the centrum semiovale showed a very pronounced status spongiosus (figure 2). The tissue consisted of cavities of varying sizes up to that of a small fingernail, but most of them were much smaller. The septa between these vacuoles (figure 3) consisted of argentophilic and collagenous fibers and abundant vessels; most of the vessels were veins, but there were also some small arteries, some capillaries, and some solid capillary buds. All of these vessels exhibited a marked overgrowth of connective tissue cells, some of which contained sudanophilic substance; there were no accumulations of such cells in the Virchow-Robin spaces. Only a few arteries possessed faintly stained and stretched elastic fibers. Most of the cavities were empty; here and there, however, they contained some glial cells or scavenger cells. There were no myelin sheaths, but a few axis cylinders and glial fibers could be verified with specific stains.

In contradistinction, a broad periventricular zone exhibited a compact degeneration, as did the peripheral parts of the centrum semiovale and the subcortical white matter. Myelin sheaths were completely absent in some places; in others a few preserved myelinated fibers were seen, but they were pale-staining and sometimes were interrupted. Axis cylinders were better preserved, but many of them were fragmented and spiral shaped. This area exhibited a pronounced fibrous gliosis, but there were almost no swollen astrocytes. No scavenger cells were found and neither metachromatic nor mucoid substance could be verified.

The arcuate fibers were not as well preserved as observation with the naked eye had suggested. The black appearance was due at least partially to an accumulation of small fiber fragments and granules which stained black with myelin sheath methods. Nevertheless, the continuity of some U-fibers was preserved everywhere, although they stained poorly. In this zone, but extending into the adjacent subcortical white matter, there were small round empty lacunae in some places without any reaction of the surrounding tissue.

Between the area of compact degeneration and that of status spongiosus there was a belt of varying thickness consisting of a rather regular network of engorged capillaries (figure 4); the interstices were filled with dense accumulations of scavenger cells containing a fatty substance, which stained brilliant red with Sudan IV. Nowhere was there a special accumulation of scavenger cells around the vessels and the Virchow-Robin spaces did not contain such cells. Only occasionally an adventitial cell contained some sudanophilic material.

In addition, there were a few large spherical or ovoid elements with three to four small marginal nuclei and a homogeneous faintly eosinophilic cytoplasm without Gitter-cell structure, reminding one of Collier and Greenfield's[2] "globoid bodies." In frozen sections they could not be verified. The oligodendroglia did not show any remarkable changes.

Finally in this area and in that of the status spongiosus, there were concretion-like hemotoxylinophilic deposits which did not stain with Kossa's or with Turnbull's method. No inflammatory reactions were found, except in two small veins in the spongy area which contained some lymphocytes in the Virchow-Robin spaces.

The process, so far described, occupied the white matter of the hemispheres at all levels. The cortex was essentially normal. True, its myelinated fibers appeared to be somewhat reduced in number and there was also a certain loss of nerve cells with resulting disturbance of the cortical architecture, but these changes were slight in comparison

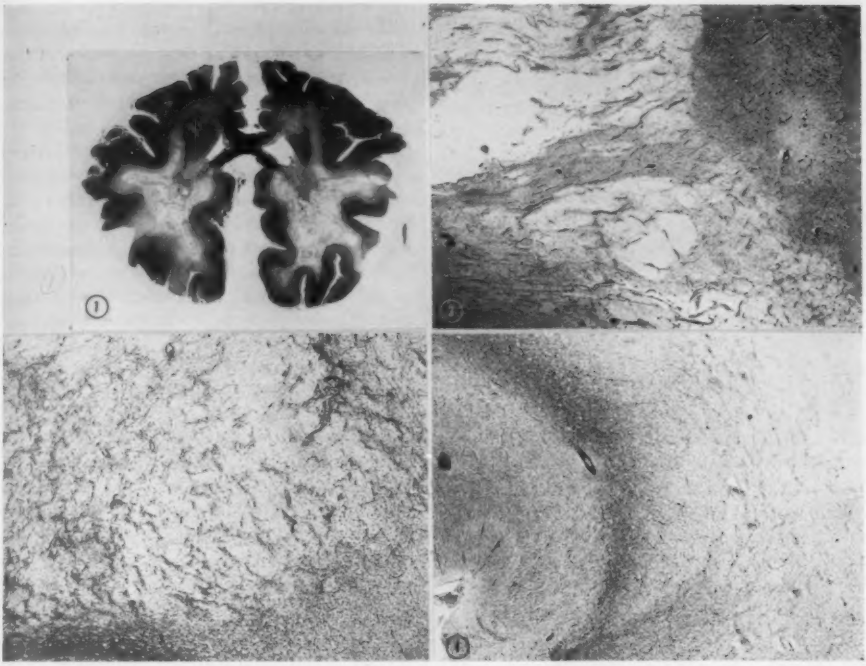


FIG. 1. Demyelination of the white matter of the hemispheres – status spongiosus – with relative preservation of the arcuate fibers. Loyez stain. *Case 1.*
FIG. 2. Status spongiosus. Overgrowth of vessels. Cresyl violet stain. *Case 1.*
FIG. 3. One of the septa in the status spongiosus. Hematoxylin and eosin stain. *Case 1.*
FIG. 4. (From left to right) Cortex – compact gliosis, most prominent in the subcortical zone – network of capillaries filled with scavenger cells. Cresyl violet stain. *Case 1.*

to the process in the white matter. There was a marked hyperemia in the cortex of most gyri.

In contradistinction, the basal ganglia, including the claustra, brainstem, and cerebellum, showed fairly well preserved structure with normal myelo- and cytoarchitecture. There were, however, multiple bilateral small foci in the reticular nuclei of the thalami extending into the posterior limb of the internal capsule on the left. Identical foci were found in the inferior colliculi, the substantia nigra (figures 5 and 6), the vestibular nuclei (figure 7), and the central white matter of the cerebellum. These foci were symmetric with regard to localization and almost symmetric in shape and size. In myelin sheath stains they resembled macroscopically the foci of multiple sclerosis. Microscopically the most outstanding feature was the excessive number of wide and tortuous capillaries, filled with erythrocytes, without changes in the walls, entering from the adjacent normal areas, together with a few fine collagenous fibers. Between them was a loose tissue resembling the status spongiosus, as described in the cerebral hemispheres, or more compact tissue with slight gliosis and a few scavenger cells. Myelin sheaths were rather scarce, whereas axis cylinders were well preserved; this dissociation was much more marked than in the lesions of the hemispheres. Most ganglion cells were normal, but some were shrunken. The foci had sharp outlines; only occasionally was there a narrow zone of partial demyelination at their edges.

In the cerebellum the surface of some folia showed dense accumulations of small cells, resembling the superficial granular layer when observed under low power, but consisting of spindle-shaped cells, the longer axes of which were parallel to the surface.

The lumbar spinal cord, the only level that could be studied, showed a moderate secondary degeneration of the crossed pyramidal tracts; no primary alterations were seen.

The leptomeninges were essentially normal, as were the larger arteries and veins.

The ventricles were not dilated. The ependymal lining of the lateral ventricles was discontinuous; if present, it sometimes consisted of several layers, not to be explained by tangential sections. There

was a marked subependymal gliosis with a vacuolar appearance, as described for the subcortical zone.

In the optic nerves the myelin sheaths were rather palely stained, without other changes. Of the remaining cranial nerves, only the third and the seventh and eighth pairs were present in our sections. They were normal.

Summary of Case 1. A male baby began to regress at the age of four months. At this time he started having seizures with stiffening and episthotonus, but without twitching. It was uncertain whether he saw and heard. When first examined at the age of five and a half months, he showed constant aimless movements, bilateral Babinski signs, and very strong tonic neck reflexes. Cortisone was given without recognizable effect. The patient died of pneumonia at the age of nine months. A detailed family history did not reveal any instance of neurologic disease. The clinical diagnosis was progressive leukoencephalopathy.

The anatomopathologic examination revealed a degenerative process of the whole white matter of the brain hemispheres. A prominent feature of the pathologic process was the pronounced status spongiosus, occupying the major part of the centrum semiovale. It was surrounded by a more compact degeneration with abundant sudanophilic scavenger cells. In the periventricular and the subcortical areas there was a marked sclerosis. In addition, multiple symmetric foci were found in the brainstem, exhibiting status spongiosus and great excess of capillaries.

DISCUSSION

As far as the pathologic findings are concerned, it is difficult to fit this first case into any of the various classifications. If we define "diffuse sclerosis" as a diffuse demyelinating process predominantly affecting the white matter of the brain, case 1 belongs to this affection. But diffuse sclerosis is by no means a homogeneous entity. Besides Schilder's disease on the one hand and the leukodystrophy on the other hand, there are some special morbid processes, so to speak, at the fringe of diffuse sclerosis. Hallervorden[3] mentioned among them the Canavan type of spongy degeneration and cases of diffuse sclerosis, with a dysplastic component. We think that our case represents another special type.

Schilder's disease may be ruled out in view of the absence of any inflammatory phenomena and also because of the topography of the process, which occupied the entire white matter of the brain. It might be a case of simple degenerative diffuse sclerosis with normal products of disintegration (Group A, 1 in Hallervorden's classification). But there are two phenomena which are at least very uncommon in this affection. The first is the great extension of status spongiosus in the centrum semiovale. True, lesions of this type have been observed, not only in Schilder's disease but also in some cases of leukodystrophy;[4–6] in these, only small areas are involved in this way, whereas in our case it is the predominant feature. In this respect, our case is similar to that of Hermel,[7] termed "encephalomyelomalacia chronica diffusa," which the author related to diffuse sclerosis. To be sure, there are some differences. The process in Hermel's case is more extensive, involving the cortex also. The axis cylinders are more severely damaged, and there is no sclerosis as in the periventricular and subcortical regions of our case. Finally, Hermel's case showed a marked hemorrhagic component, which is absent in our case. But the prominent feature, the softening in the form of a status spongiosus with extensive proliferation of capillaries, is identical in both cases. Hermel's figure 2 could have been taken from our case.

Of course, status spongiosus may be caused by one of several mechanisms. Fluid exudation or transudation may be an important factor, as in Canavan's type of diffuse sclerosis. The process in Hermel's case and in our case certainly has nothing to do with this type of disorder. According to Braunmühl,[8] a status spongiosus may result from dehydration. In the case discussed here, as Spielmeyer[9] suggested, an unusually violent destruction of nervous tissue with a deficient glial reaction is probably responsible. Our case exhibits transitions from status spongiosus through a more solid degeneration to typical sclerosis. Thus, the softening seems to be the most severe lesion caused by the underlying disorder.

The second uncommon feature of our case is the presence of symmetric foci in several levels of the brainstem, although no signs or symptoms to suggest brainstem lesions were

observed clinically. In myelin sheath stained sections, they have a macroscopic aspect similar to that of multiple sclerosis. Their histopathologic appearance is that of the status spongiosus of the brain, with an even more pronounced vascular proliferation. Multiple sclerosis-like foci are a frequent finding in Schilder's disease, but appear also in some cases of leukodystrophy.[1,4,6,10] Histopathologically, such foci are similar to those of multiple sclerosis. In view of the tendency to a softening process in our case, however, it is perhaps not surprising to find this picture in the small foci, too. Foci showing softening have also been described in a few cases of multiple sclerosis.

Another striking feature of the brainstem foci of our case 1 is their symmetry. Again, this is an occurrence observed in some cases of multiple and diffuse sclerosis.[10,11] We may conclude that none of the particularities is completely alien to diffuse sclerosis, but taken together they are sufficient to give our case a place apart.

In Hermel's case, no small foci were observed. But the medulla oblongata and cerebellum could not be examined, nor can we be sure that the remaining parts of the brainstem were studied. In any event, they were not mentioned.

On the other hand, the small symmetric foci of our case were very similar to those found by Leigh[12] in his case of "subacute necrotizing encephalomyelopathy." These in turn resemble experimental findings in monkeys treated with quinoline compounds.[13] Since Leigh's paper, six cases of the same type have been published.[14,15] The findings in our case are identical with those of these seven cases. The symmetry of the foci, their localization in the brainstem predominantly, but not exclusively, in the gray matter, histopathologically the softening and demyelination (in the original sense of loss of myelin sheaths with better preservation of the axis cylinders), the scarcity of astrocytic reaction, the excess number and tortuosity of capillaries, and the striking preservation of at least part of the ganglion cells are features common to our case and those of the literature.

With regard to the increased number of vessels, Feigin and Wolf,[14] as well as Richter,[15]

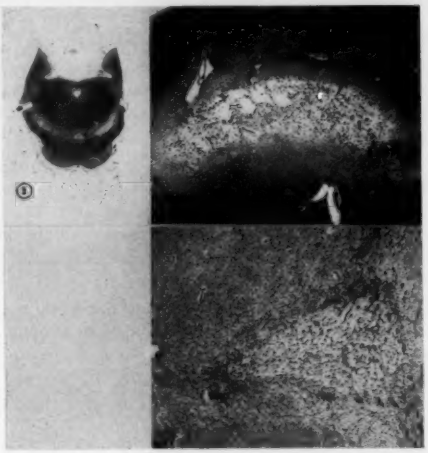


FIG. 5. Symmetric softening of the substantia nigra. Loyez stain. *Case 1.*
FIG. 6. Substantia nigra, showing softening with status spongiosus. Cresyl violet stain. *Case 1.*
FIG. 7. Nucleus vestibularis, showing beginning softening and overgrowth of capillaries. Cresyl violet stain. *Case 1.*

suggested it might be only apparent due to the loss of nerve parenchyma, but it exceeds by far what we usually see in encephalomalacia. We think, therefore, that we are dealing with a peculiarity of the disorder in question.

As in the other seven observations, the substantia nigra was involved in our case and, again, as in all of them, the mammillary bodies were intact. The inferior olive, seat of the lesion in three cases, was normal in our case, and the symmetric foci in the central white matter of the cerebellum are somewhat unusual. But the main difference concerns the brain, which in six cases of the literature showed only slight and uncharacteristic changes, if any. Only in Richter's[14] third case more severe cerebral lesions were found. But they were predominantly localized in the cortex; insofar as the white matter participated, it was obviously by extension of the cortical affection. Furthermore, in both the cortex and the subcortical white matter the process was patchy, not diffuse. In contradistinction, in our case the cortex was essentially normal and the U-fibers were relatively preserved. Richter, in his case, rightly speaks of "polioencephalopathy." We had to call the cerebral process of our case a "leukoencephalopathy."

Haymaker,[16] in the discussion to Richter's paper, as well as Leigh,[12] pointed to the similarity of the findings with those of Wernicke's disease; Feigin and Wolf[14] even applied that name to their cases. But in none of the cases, including our own, was there any evidence of a nutritional defect, let alone a thiamin deficiency. Therefore, Richter,[13] in view of the identical picture he found in his monkeys treated with quinoline compounds, preferred the hypothesis of a toxic agent, and Feigin and Wolf[14] assumed a congenital disturbance of metabolism, a "physiological malformation."

In any case, it is too early to analyze the etiopathogenesis of such a single and exceptional case as ours. May it suffice to characterize the process as a combination of features of leukodystrophy, of Hermel's encephalomyelomalacia, and of Leigh's subacute necrotizing encephalomyelopathy.

Among the remaining findings in case 1, the failure of the sudanophilic macrophages to accumulate around the vessels and in the Virchow-Robin spaces is worth mentioning. While the transformation of the products of myelin breakdown into neutral fat takes place in the usual way in macrophages of microglial origin, the transport of this material toward the mesodermal tissue, and therefore probably its elimination, is deficient. The cause of this defect is difficult to explain.

SUMMARY OF CLINICAL DATA — CASE 2

A white female child was first seen at the age of 24 months because of convulsions, stiffness of the extremities, and decline of development beginning at least at the age of 20 months, although the child had been slow previously.

This child was the product of her mother's first pregnancy, which was normal in all respects, as was the delivery at term. Jaundice was noted on the second or third day, the mother being Rh negative and the father Rh positive, but the mother was said to have no anti-Rh titer during pregnancy. A single transfusion was given during the newborn period. Birth weight was 7 pounds, 14 ounces. Development was slow. The baby did not hold her head up until three weeks and then progressed more rapidly, sitting with support at four months. It was observed that her social responses were less and that she was more lethargic than her younger sibling at the same age. She crept at eight months and tried to stand at ten months but had some difficulty because her legs were becoming stiff. A diagnosis of cerebral palsy was made at 17 months. At the age of 19 months she was able to feed herself, crept, said four or five words, and formed one or two two-word phrases. She played with toys and was able to dial a toy telephone. She turned pages in a book and identified pictures of animals in books and on television. Slight twitching of the legs was noted.

Family history. The mother, who was 25 and well, was an orphan and her family history is unknown. The father was 27 and well. A paternal aunt, now aged 27 years, developed ptosis, weakness, and disability in walking after the birth of her first child and periodically has recurrence of such symptoms. One female sibling of the child, aged eight months, was thought to be normal in all respects.

Present illness. An obscure febrile illness developed in August 1954 at the age of 20 months, with fever of 102° F., anorexia, and constipation. Penicillin was prescribed. The infection lasted about two weeks. During this period, the child stopped using her hands, her eyelids drooped, and she had difficulty in swallowing solid foods and had to go back to strained foods and liquids. She was limp and no longer able to sit up. Generalized seizures began, consisting of extension of the head, stiffening of the arms and legs, and urination, with possible loss of consciousness. These continued daily for two weeks, gradually decreased to one every two or three days, and stopped at about the age of 23 months.

Physical examination. General examination was normal and revealed that the height was 33 inches, the head circumference 17½ inches, and the weight 26 pounds. There was spastic tetraplegia with hyperactive reflexes, ankle clonus, and bilateral Babinski signs. Strong tonic neck reflexes were seen in either direction. The motor cranial nerves and the eyegrounds were normal.

Laboratory work was within normal limits, with the exception of lumbar puncture which produced spinal fluid with a total protein of 131 mg. per 100 ml. but no cells. The ventricular fluid obtained at the end of the pneumoencephalogram contained only 63 mg. per 100 ml. A subsequent spinal puncture again produced fluid with no cells, but a total protein of 96 mg. per 100 ml. Electroencephalogram was abnormal, showing diffuse slowing in all leads, most prominent in the left precentral and occipital. A pneumoencephalogram showed a normal ventricular system and normal surface air pathways.

Cortisone was begun and given in doses of 250 mg. per day for six days, then gradually cut down at discharge to 150 mg., on which the child was to continue for three weeks. No improvement was noted on this regimen.

The child was subsequently followed in the neurology clinic and cortisone gradually was withdrawn over a six-week period. She became increasingly irritable and difficult to feed but had no seizures. She was essentially decerebrate when seen at the age of two years and 11 months. The

retrospective impression was that the child had developed reasonably normally until about the age of ten months, although her responses may have been somewhat less than those of her younger sibling at the same age. The decline in performance was clear at least from the febrile illness at 20 months, and very probably from about the time her legs became stiff at ten months. The clinical diagnosis was a progressive leukoencephalopathy of the Schilder group. The patient was admitted to a state institution where she died at the age of three years.

Autopsy. There were flexion deformities of the hands and a bilateral talipes equinus. The liver showed focal fatty infiltration. The remaining body organs were macroscopically normal.

The brain weight was 830 gm. (normal 1,141 gm.). The convolutions were slightly smaller than normal.

After fixation the central white matter of the frontal lobes showed a peculiar grayish-yellow mottling. This aspect was even more prominent in the occipital lobes. There were symmetric clefts of dehiscence in the external capsule, which inferiorly extended along the lenticulostriate vessels. In this area the white matter showed the same pattern as that of the frontal lobes. The putamen was mottled and discolored. The cerebellum was very firm to palpation.

The microscopic examination of the body organs (only paraffin sections were available) did not reveal any significant changes.

An increased number of Schwann cells was found in the sciatic nerve, but there was no evidence of neuronal degeneration.

Microscopic findings. Loyez sections, when observed with the naked eye, showed absence of myelination in most parts of the brain, except for most of the arcuate fibers, the globus pallidus, Forel's fields, and the mammillothalamic tracts (figure 8). The centrum semiovale had a spotty appearance, with alternation of grayish and yellowish areas (Loyez). Microscopically the grayish areas showed a dense dissemination of grayish black granules, often arranged in rows corresponing to the course of myelinated fibers. There were also some better preserved but palely stained myelin sheaths of varying density, sometimes fragmented or with a bead-like appearance. The yellowish areas were round or elongated, mostly with a wide central vessel with dilated Virchow-Robin spaces. These areas contained neither myelin fibers nor black granules.

The arcuate fibers were better preserved; however, many of them were not continuous but consisted again of rows of granules. The same was true for the radial fibers entering the cortex. No other cortical myelinated fibers were stained in Loyez sections. The corpus callosum and the internal capsule did not contain any stained myelinated fibers. In the basal ganglia, the striae of the striatum were thin and rarefied and their fibers stained palely. The pallidum showed a much better, although not completely normal, myelination. The thalamus was almost devoid of myelinated fibers. In the basal ganglia, the striae of myelinated fibers were rarefied and pale staining. In the central white matter of the cerebellum, only some scattered single myelinated fibers were seen. The white matter of most cerebellar folia was demyelinated, too, but some of the folia contained fairly well preserved myelinated fibers.

It should be noted that there was a striking difference between the results of Loyez's and of Spielmeyer's methods. The latter showed in many areas more and better stained myelinated fibers than the former.

In the Bielschowsky silver impregnation the axis cylinders showed, on the one hand, better preservation than the myelin sheaths; on the other hand, they were rarefied in comparison with the normal picture. In some places the silver-impregnated fibers were discontinuous and fragmented.

The cytoarchitecture of the cortex was essentially normal. The cortical ganglion cells were well stained and without significant changes. Rather numerous ganglion cells were found in the subcortical white matter. The ganglion cells of the thalamus were very pale, with indistinct outlines; those of the striatum were somewhat better preserved.

Lesions of a more severe type were found in some areas of the centrum semiovale and in the pallidum. Here the structure in cresyl-violet and hematoxylin and eosin stained sections was very indistinct, with shadowy cells and almost unstained nuclei. In such areas only the capillaries were outstanding.

While in the parts just mentioned the tissue continuity was preserved and the general structure still recognizable, an even more pronounced destruction was found in the claustra bilaterally. The dorsal parts of these nuclei were occupied by elongated cavities, lined by the external and extreme capsules, both of which appeared macroscopically grayish-black due to the presence of abundant Loyez-stained granules (figure 8). The ventral parts exhibited a status spongiosus in which, except for capillaries, only a few ganglion and glial cells were preserved.

In all regions showing absence or rarefaction of myelinated fibers, a striking feature was the presence of round or slightly ovoid cellular elements the size of pyramidal cells (figure 9). In some of them, nuclei were not visible; if present, they were pale and ill defined, either in central or in peripheral position. As far as the cytoplasm is concerned, two types were distinguished. Type A was finely granular or almost homogeneous and had reasonably sharp outlines. The granules stained deep black with Loyez and Spielmeyer methods and were pronouncedly eosinophilic in hematoxylin and eosin sections. Type B had blurred outlines and coarser unequal granules which stained grayish with myelin methods and purple to violet in hematoxylin and eosin. The

granules of both types did not stain with Sudan IV; at most they showed a dirty yellow hue, but they were pronouncedly PAS positive.

When tested with acetic-acid-cresyl-violet for metachromasia in frozen sections, all these elements appeared brownish. Type B cells were diffusely and loosely scattered throughout the demyelinated areas, whereas those of Type A were mostly arranged in groups, predominantly located in the subcortical white matter and in some subependymal areas. No typical sudanophilic scavenger cells were found, with two exceptions: 1) everywhere in the granular layer of the cerebellar cortex there were some round granular bodies showing slight brownish metachromasia with cresyl-violet, but also a yellowish orange hue in Sudan-IV sections; 2) in a small circumscribed, fairly well myelinated area of the cerebellar central white matter, there were numerous cells of microglial structure, the processes of which contained brilliant red sudanophilic granules which showed no metachromasia (figure 10). In contradistinction, the Virchow-Robin spaces of almost all vessels of the demyelinated areas were filled with typical sudanophilic macrophages (figure 9). In addition, there were a few lymphocytes in these spaces.

There was a very pronounced proliferation of astrocytes; many of them were particularly large, often with two marginal nuclei. Frequently the cytoplasm of such astrocytes was indented by one of the atypical scavenger cells, separated from it by a clear crescent-shaped gap (figure 11). Thus the cell body became concave-convex. Sometimes two symmetric astrocytes surrounded a granular body in almost its entire circumference (figure 12). Holzer technic revealed an intensive isomorphous and anisomorphous fiber gliosis. Oligodendroglia cells were definitely diminished in number, moreso in areas devoid of myelin sheaths than in partially demyelinated ones.

In addition to the atypical scavenger cells, some ganglion cells, especially those of the nucleus dentatus, also contained a metachromatic substance which stained brownish in acetic-acid-cresyl-violet sections, but this material showed a yellowish-red color in Sudan stains; some of the granules stained black with Spielmeyer. However, no swelling of these ganglion cells could be verified.

The intracerebral vessels showed only a slight swelling of the endothelial cells. The lumina of both superior cerebellar arteries were filled with recent thrombi, although the walls were unchanged. Small perivascular hemorrhages were seen in the cortex of the left first frontal gyrus and in the left mammillary body. Finally, there was bleeding into the posterior horn of the right lateral ventricle. The otherwise well preserved ventricular ependyma was interrupted in a rather circumscribed area.

The leptomeninges exhibited increased numbers of fibrocytes and fibroblasts in some places, but showed no inflammatory reaction anywhere.

Of the cranial nerves, only the left acusticus and both oculomotorii were present in our sections. Whereas the former appeared unchanged, the latter showed extensive demyelination; only in two small bundles were myelin fibers fairly well preserved. In the demyelinated bundles a marked overgrowth of Schwann cells was seen. Between them there were Loyez-stained scavenger cells like those of the brain. The optic tracts showed demyelination to a much lesser degree, with a moderate number of the atypical scavenger cells and with moderate proliferation of astrocytes. The optic nerves were not to be found in our sections.

Summary of Case 2. A female child showed some retardation of mental development at the age of ten months. At 20 months of age she began to have generalized convulsions with extension of the head and rigidity of the extremities. At the age of two years she presented a spastic tetraplegia, and 11 months later she was essentially decerebrate. She died at the age of three years. The family history was negative except for a recurrent apparently organic nervous disease of a paternal aunt, dating from the birth of her first child. The clinical diagnosis of our case 2 was progressive leukoencephalopathy of the Schilder group.

The pathologic changes of this case were essentially those found by numerous previous authors in cases of so-called "metachromatic leukodystrophy." The atypical products of myelin disintegration showed a pronounced brownish metachromasia in frozen sections treated with cresyl violet. The scavenger cells of the Virchow-Robin spaces showed the same metachromasia, in addition to their brilliant red color in scarlet red stain. The same was true of the ganglion cells of the dentatum. Many of the proliferated astrocytes were indented by the atypical scavenger cells. A circumscribed focus of the cerebellar white matter contained typical scavenger cells with sudanophilic products. Finally, there was a bilateral symmetric softening of the claustra.

DISCUSSION

The pathologic findings of the second case are in all essential respects identical with those described by several authors in cases of leukodystrophy with "prelipoid" metachromatic products of disintegration.[17–23] Our case belongs to the group with marked predominance of the metachromatic material.[19] Unfortunate-

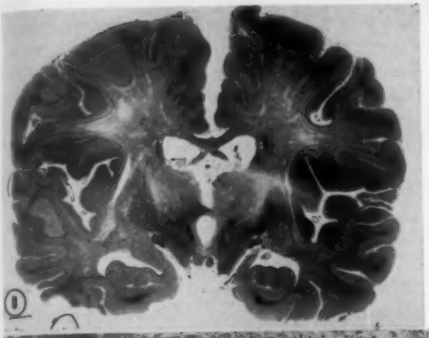


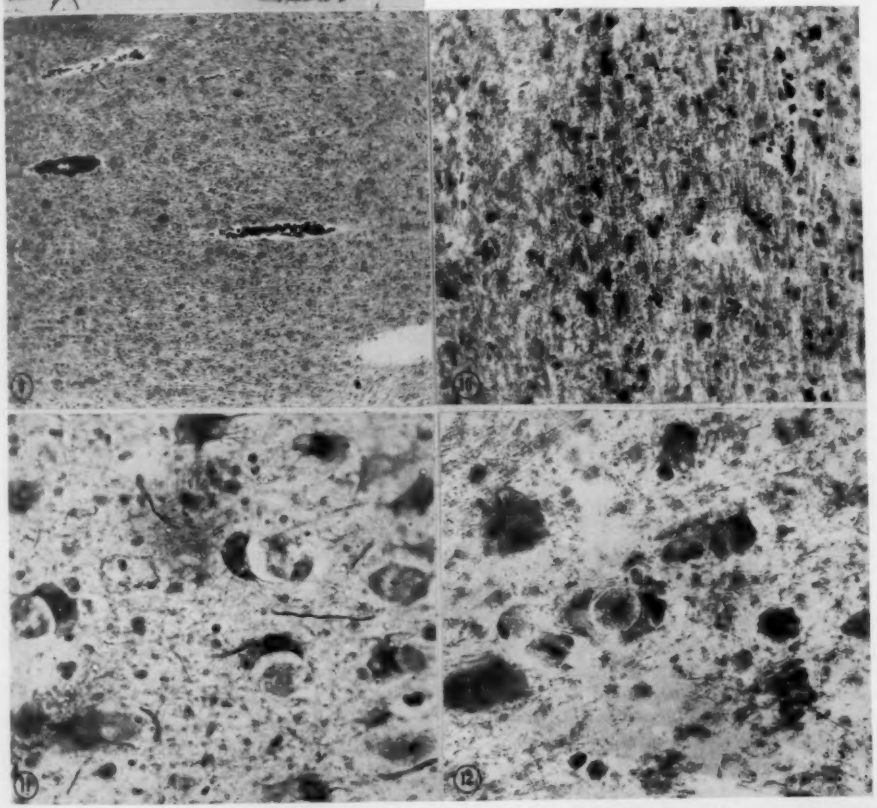
FIG. 8. Demyelination of white matter of the hemispheres. Preservation of many arcuate fibers. Symmetric softening of claustra. Loyez stain. *Case 2.*

FIG. 9. White matter of hemispheres. Pale yellow staining of the atypical scavenger cells, bright red staining of the cells in the Virchow-Robin spaces. Scarlet red stain. *Case 2.*

FIG. 10. Focus of sudanophilic scavenger cells of microglial origin, stained brilliant red in scarlet red sections. *Case 2.*

FIG. 11. Indentation of astrocytes by atypical scavenger cells. Penfield's method. *Case 2.*

FIG. 12. One scavenger cell almost completely surrounded by the cytoplasm of two astrocytes. Alzheimer-Mann stain. *Case 2.*



ly our observation does not add anything new to the knowledge of the abnormal metabolism underlying this process, or to the question of a generalized metabolic disorder versus a functional deficiency of the central nervous system, especially of the oligodendroglia.

Emphasis may be put on the brownish color of the atypical substance when stained in frozen sections with cresyl violet in acetic acid solution, as indicated by Diezel and Richardson.[24] Absence of metachromasia should be asserted in no case of leukodystrophy unless

this method has a negative result, or frozen sections have been used.[1,3,25] As first pointed out by Scholz[26] and by Van Bogaert and Scholz,[27] the atypical material existing in the scavenger cells of nervous tissue is unstainable or very faintly stained with Sudan. In contradistinction, the elements accumulated in the Virchow-Robin spaces exhibit a brilliant red color in Sudan sections. Whereas this behavior may also be verified in our case 2, interestingly enough the cells of the Virchow-Robin spaces show, at the same time, metachromasia as well as a positive PAS reaction. We may conclude that even in the vascular cells only a certain portion of the lipids is broken down to neutral fat.

A similar behavior has been noted in our case regarding the lipids found in the ganglion cells of the nucleus dentatus. Changes of this kind, according to some authors, point to a relationship between leukodystrophy and amaurotic idiocy.[21,28] In our case, however, the special localization in the dentatum—which seems to be typical—and the absence of swelling of the ganglion cells show these deposits to be rather different from those we find in amaurotic idiocy.

An unusual finding is the presence of typical sudanophilic macrophages of microglial origin in a circumscribed area of the cerebellar white matter. While the nature of this process is obscure, we are entitled to conclude—in agreement with Patrassi[29]—that there is no generalized insufficiency of the microglia as Einarson and Neel[19] supposed. A similar finding could be verified in our case of unusual leukodystrophy with megalencephaly.[30]

Another remarkable feature of our case is the peculiar behavior of the astrocytes in the presence of atypical scavenger cells. There is no phagocytic activity. On the contrary, the macroglia seems to suffer a passive damage by those elements. One gets the impression that a cytolytic activity springs from the pathologic material (figures 10 and 11). Similar but not identical cases apparently have been reported.[31]

The number of oligodendroglia cells is definitely reduced in the demyelinated areas of our case 2. Findings of this order often have been considered to be the primary factor in leukodystrophy,[32,33] but so far the possibility has not been ruled out that they represent a consequence rather than a cause of the pathologic process.[10] The fact that we found the reduction of these cells more pronounced in areas devoid of myelin sheaths than in partially demyelinated regions perhaps is more in favor of the first alternative in our case.

The last special feature of our second case is the bilateral symmetric softening of the claustra. Whereas these lesions have a certain similarity to the symmetric foci of our first case, the localization in the claustra seems to have a special meaning. This phenomenon has been seen in several other cases of diffuse sclerosis. Thus we are not dealing with a chance effect, but with a peculiar relationship between the underlying process and the aforementioned ganglion. This subject will be discussed more thoroughly in a separate paper.

SUMMARY

Two cases of progressive leukoencephalopathy in children are reported. In both of them the general clinical diagnosis of this disorder could be made but, as in most of the other cases, the special type was not verified clinically. In neither case was there any similar disease in other members of the families.

The pathologic examination revealed in case 1: a nine month old male child with a combination of features of leukodystrophy, Hermel's encephalomyelomalacia, and Leigh's subacute necrotizing encephalomyelopathy. In case 2, a three year old girl, findings typical of the so-called "metachromatic leukodystrophy" were verified. Some special findings consisted of a peculiar relationship between the proliferated astrocytes and the macrophages containing the atypical products, of the metachromasia of the cells in the Virchow-Robin spaces, of the presence in the cerebellar white matter of a degenerative focus with typical sudanophilic products of myelin-breakdown, and, finally, of bilateral and symmetric softenings of the claustra.

REFERENCES

1. Greenfield, J. G.: The classification of diffuse demyelinating sclerosis of the brain on the basis of pathogenesis. Folia psychiat. neerl. 53:255, 1950.
2. Collier, J., and Greenfield, J. G.: The encephalitis periaxialis of Schilder. Brain 47:489, 1924.
3. Hallervorden, J.: Die degenerative diffuse Sklerose.

In Henke-Lubarsch Handbuch der Speziellen Pathologischen Anatomie und Histologie, Band XIII, Teil 1, p. 716. Springer-Verlag, Berlin, 1957.

4. Bielschowsky, M. and Henneberg, R.: Ueber familiaere diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria). J. f. Psychol. u. Neurol. 36: 131, 1928.
5. De Lange, C.: Ueber die familiaere infantile Form der diffusen Gehirnsklerose (Krabbe). Ann. Paediat. 154: 140, 1940 and 155:277, 1940.
6. Frank, J.: Diffuse Erkrankung des Hemisphaerenmarks und Allgemeinerkrankung der myelinhaltigen Strukturen des Zentralen Nervensystem. Arch. Psychiat. 179:146, 1947/48.
7. Hermel, H.: Ueber einer Fall von Encephalomyelomalacia chronica diffusa bei einem 4-jährigen Kind. Deutsche Ztschr. Nervenh. 68-69:335, 1921.
8. v. Braunmuhl, A.: Alterserkrankungen des Zentralnervensystems. Senile Involution. Senile Demenz. Alzheimersche Krankheit. In Henke-Lubarsch Handbuch der Speziellen Pathologischen Anatomie und Histologie, Band XIII, Teil 1, p. 337. Springer-Verlag, Berlin, 1957.
9. Spielmeyer, W.: Histopathologie des Nervensystems. Springer, Berlin, 1922.
10. Russel, D., and Tellerman, K. H.: Familial progressive diffuse cerebral sclerosis of infants. Arch. Dis. Childhood 12:71, 1937.
11. Döring, G.: Zur Pathologie und Klinik der Entmarkungsencephalomyelitis. Deutsche Ztschr. Nervenh. 153:73, 1942.
12. Leigh, D.: Subacute necrotizing encephalomyelopathy in an infant. J. Neurol., Neurosurg. & Psychiat. 14:216, 1951.
13. Richter, R.: The effect of certain quinoline compounds upon the nervous system of monkeys. J. Neuropath. & Exper. Neurol. 8:155, 1949.
14. Feigin, I., and Wolf, A.: A disease in infants resembling chronic Wernicke's encephalopathy. J. Pediat. 45:243, 1954.
15. Richter, R.: Infantile subacute encephalopathy with predilection for the brain stem. J. Neuropath. & Exper. Neurol. 16:281, 1957.
16. Haymaker, W.: Discussion of Richter's paper.[12]
17. Witte, F.: Ueber pathologische Abbauvorgänge im Zentralnervensystem. München. med. Wchnschr. 1:69, 1921.
18. Kaltenbach, H.: Ueber einen eigenartigen Markprocess mit metachromatischen Abbauprodukten bei einem paralyse-aehnlichen Krankheitsbild. Ztschr. ges. Neurol. u. Psychiat. 75:138, 1922.
19. Einarsen, L., and Neel, A. V.: Beitrag zur Kenntnis sclerosierender Entmarkungs-processe im Gehirn mit besonderer Berücksichtigung der diffusen Sklerose. Acta Jutlandica 10:1, 1938.
20. Jervis, G. A.: Early infantile "diffuse sclerosis" of brain (Krabbe's type). Am. J. Dis. Child. 64:1055, 1942.
21. Norman, R. M.: Diffuse progressive metachromatic leuco-encephalopathy. Brain. 70:234, 1947.
22. Adams, R. D., and Kubik, C. S.: Morbid anatomy of the demyelinating diseases. Am. J. Med. 12:510, 1952.
23. Leslie, D. A.: Diffuse progressive metachromatic leucoencephalopathy. J. Path. & Bact. 64:841, 1952.
24. Diezel, E. A. and Richardson, E. P.: Histochemical and neuropathological studies in leucodystrophy. J. Neuropath. & Exper. Neurol. 16:130, 1957.
25. v. Hirsch, T. and Pfeiffer, J.: Ueber histologische Methoden in der Differentialdiagnose der Leucodystrophieen und Lipoidosen. Arch. Psychiat. 194:88, 1955.
26. Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiaerer diffuser Hirnsklerose in Kindesalter. Ztschr. ges. Neurol. u. Psychiat. 99:651, 1925.
27. van Bogaert, L. and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiaeren diffusen Sklerose. (Familiaere juvenile Leucodystrophie). Ztschr. ges. Neurol. u. Psychiat. 141:150, 1932.
28. Wicke, R.: Ein Beitrag zur Frage der familiaeren diffusen Sklerose einschliesslich der Pelizaeus-Merzbacherschen Krankheit und ihrer Beziehung zur amaurotischen Idiotie. Ztschr. ges. Neurol. u. Psychiat. 162:741, 1938.
29. Patrassi, G.: Diffuse Gehirnentmarkungen und sogenannte Encephalitis periaxialis diffusa (Schilder). Arch. path. Anat. 281:98, 1931.
30. Wohlwill, F. J., Bernstein, J. and Yakovlev, P.: A case of unusual, presumably familial leucodystrophy with megalencephaly. J. Neuropath. & Exper. Neurol. 16:129, 1957.
31. Blackwood, W., and Cumings, J. N.: A histological and chemical study of three cases of diffuse sclerosis. J. Neurol., Neurosurg. & Psychiat. 17:33, 1954.
32. Greenfield, J. G.: A form of progressive cerebral sclerosis in infants, associated with primary degeneration of the interfascicular glia. Vol. Jubilaire Marinesco, 1933, p. 257.
33. Brain, W. R., and Greenfield, J. G.: Late infantile metachromatic leuco-encephalopathy with primary degeneration of the interfascicular oligodendroglia. Brain 73:291,1950.

Demonstration of carotid occlusion by small dose arteriography

W. H. Oldendorf, M.D.

BETWEEN January 1956 and April 1957 small dose arteriography was performed on 50 patients suspected of having internal carotid artery occlusion. Patency was established in 41 cases and failure to fill was observed in nine cases. No serious complications were noted.

This investigation was undertaken to determine how small an amount of arteriographic medium would dependably visualize the carotid system, using a single exposure and standard materials. With precise timing, 0.5 cc. of 50 per cent Hypaque was found adequate to visualize the bifurcation. Without excessively critical timing, the entire carotid system could be dependably visualized by 2 cc. of medium. Using 2 cc. the following technic was employed.

TECHNIC

The patient is given 75 to 100 mg. Demerol intramuscularly. He is then placed in the supine position. A single 10 by 12 inch grid-cassette is placed adjacent to the side of the head to be injected and pushed caudally as far as possible. Ideally the needle will be seen on the film. The area of the cassette covering the neck may be covered with a 4 mm. thick sheet of aluminum to partially equalize head and neck exposure.

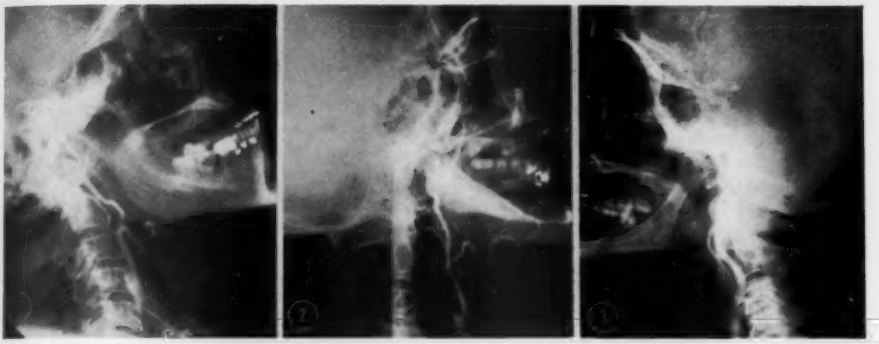
After skin antisepsis and draping, a procaine block is performed of the skin and region of the common carotid, 2 to 4 cm. below the bifurcation. About 3 cm. below the bifurcation, a sharp bevel 20 gauge 1.5 inch needle held between thumb and forefinger is introduced perpendicularly through the anterior and posterior walls of the artery. The needle is depressed about 45 degrees and slowly withdrawn. When the lumen of the tip of the needle reenters the arterial lumen, blood appears. Shortly thereafter a definite end-point is reached in the form of an impulse as the artery springs open. The needle is then advanced about 1 cm. upward, attempting to parallel the long axis of the vessel. A 5 cc. syringe containing 2 cc. of 50 per cent Hypaque is attached to the needle and injected during a one to one and a half second period. Immediately prior to the end of the injection, a single exposure is made using lateral skull technic. The needle is withdrawn and light digital compression is applied for 30 seconds. No compression dressing has been found necessary.

CASE REPORTS

Case 1. A 54 year old man was admitted on March 1, 1956 with chief complaints of sudden onset of speech disturbance and confused behavior. He had noted some weakness of the right hand and pain behind both eyes two weeks previously. On admission there was a central retinal artery thrombosis on the left. For approximately one day a temporal hemianopsia could be demonstrated in the right eye. A right hemiparesis was noted and there was diminution of the left carotid pulsation in the region of the bifurcation. Within several days there was clearing of the hemiparesis, confusion, and right temporal field defect. When adequate fields could be performed, it was shown that the left eye was blind, except for an island of intact vision in the left lower quadrant between 30 degrees to 50 degrees from the center of the field. Small dose carotid visualization confirmed the clinical impression of left internal carotid occlusion (figure 1).

Case 2. A 69 year old man had sudden onset of aphasia and minimal right hemiparesis five years before admission. Both symptoms cleared rapidly but never completely. The chief complaint on admission was progressive confusion over a period of one year. Following admission he fell to the floor without apparent injury. The next day he showed right hemiparesis and aphasia, which partially cleared within two days, when he again fell without apparent injury and was immediately hemiplegic on the right and aphasic. There was

From the neurology section, Veterans Administration Center, Los Angeles, and the department of medicine, University of California Medical Center, Los Angeles, California. Presented in part before the Los Angeles Society of Neurology and Psychiatry, May 13, 1957.



GAUGE	DIAMETER mm. INT.	EXT.	RESIST. to FLOW (relat.)
17	1.07	1.47	.4
18	0.84	1.25	1
20	0.57	0.89	5

④

FIG. 1. *Case 1.* Occlusion diagnosed on clinical findings of sudden left cerebral deficit and left retinal ischemia.

FIG. 2. *Case 2.* Occlusion diagnosed by small dose arteriography in a patient who was thought to have intracranial thrombosis.

FIG. 3. *Case 3.* Occlusion suspected on the basis of numerous transient episodes thought to be due to cerebral ischemia. On the original film an indentation suggesting a plaque can be seen on the posterior wall of the internal carotid 1 to 2 cm. above the bifurcation.

FIG. 4. Dimensions of needles commonly used in cerebral arteriography and the approximate calculated resistance to flow per unit length. (Dimensions were supplied by Becton, Dickinson and Company, Rutherford, New Jersey.)

no visible retinal abnormality. Small dose arteriography demonstrated internal carotid occlusion with filling of the siphon from the ophthalmic artery (figure 2).

Case 3. A 65 year old man was admitted five months after the onset of a classic syndrome of left posterior inferior cerebellar artery. In addition to the static symptoms referable to the left medulla, he had noted innumerable transient disturbing attacks of simultaneous paresthesias of the left angle of the mouth and left hand. No ocular symptoms were noted. There was no visible retinal abnormality. Right small dose carotid arteriography demonstrated patency of the internal carotid. An indentation incompletely obstructing the lumen could be seen on the original film immediately beyond the bifurcation and was felt possibly to represent an arteriosclerotic plaque (figure 3).

DISCUSSION

Three cases are described which illustrate the clinical value of small dose arteriography in establishing or excluding internal carotid occlusion. In case 1, the clinical impression strongly favored carotid occlusion before arteriography. In case 2, the lack of evidence of retinal ischemia on clinical grounds suggested that the vascular defect was above the carotid siphon. In case 3, the obstruction was suspected but not demonstrated by arteriography.

Many clinically suspected occlusions are not confirmed angiographically because of justifiable hesitancy to subject a patient with known vascular disease to a potentially hazardous procedure. Complications presumably result from the effects of the injected contrast medium and the physical manipulation involved in the arteriopuncture. As the irritative qualities of the media are improved and the injected volume reduced, the total trauma approaches that of simple arteriopuncture. Crawford[1] emphasized that the arteriopuncture itself is responsible for some of the morbidity seen following angiography. From this it follows that angiography with a small needle and the injection of small amounts of dye is probably safer than when done with larger needles and dye volumes.

The relationships of the quality and volume of dye used and postangiographic complications have been commented upon by Frovig,[2] Perese,[3] Sedzmir,[4] and others. These authors recommend as little dye as is necessary for films of diagnostic quality. Satisfactory intracranial detail has been reported by Dunn,[5] using 3 cc. of Hypaque. There is general agreement that the recently introduced 50 per cent

sodium diacetrizoate (Hypaque) is less irritating than others in common use.[6,7]

Without critical timing, 2 cc. of this medium will dependably visualize the entire carotid system with a single exposure, using standard materials. As the volume of dye is reduced below 2 cc., the timing of the exposure becomes exceedingly critical for complete carotid visualization. However, with precise timing, 0.5 cc. of dye demonstrates the bifurcation. This volume would probably suffice for the entire internal carotid if a rapid sequence device were available.

The use of only 2 cc. of medium permits the employment of a small diameter needle, with a consequent reduction of trauma to the artery wall. There is a calculated relative resistance to flow of approximately 1:5 for 18 and 20 gauge needles of equal length (figure 4). In the application described here, the relative rates of flow are partially equalized by the greater hydrostatic pressure attainable in a smaller syringe with a given injection force. The rate of injection should be such that the upper end of the dye column appears beyond the siphon.

The smaller needle obviates the need for prolonged digital or dressing compression, elminating this as a possible source of post-injection ischemia. In the first 50 cases visible hematoma occurred in only one case.

Puncture near the bifurcation is avoided, eliminating trauma at this common site of thrombosis. If injections are made near the bifurcation, a clear orientation of the major vessels is frequently difficult. When only the external carotid fills there is the possibility that it has been injected directly beyond the bifurcation. Even though the prominently pulsating carotid sinus is often tempting, it has been our practice to go 2 to 3 cm. below so that a definite segment of common carotid appears on the film.

CONCLUSIONS

1. A small dose arteriographic technic is described which visualizes only the carotid system, attempting to minimize chemical and physical trauma.

2. Although no morbidity has been noted in this series of 50 cases, the number is too small to establish the safety of this procedure relative to full scale arteriography.

REFERENCES

1. Crawford, T.: The pathological effects of cerebral arteriography. J. Neurol., Neurosurg. & Psychiat. 19: 217, 1956.
2. Frovig, A. G., and Koppang, K.: Cerebral complications following percutaneous carotid angiography with contrast media of the diodrast group. Acta psychiat. et neurol. 28:339, 1953.
3. Perese, D. M., Kite, W. C., Bedell, A. J., and Campbell, E.: Complications following cerebral angiography. Arch. Neurol. & Psychiat. 71:105, 1954.
4. Seidzimir, C. B.: Towards safer angiography. J. Neurosurg. 12:460, 1956.
5. Dunn, J., Jr., Vihlein, A., and Holman, C. B.: The use of sodium diacetrizoate in cerebral angiography. J. Neurosurg. 13:627, 1956.
6. Whiteleather, J. E., and DeSaussure, R. L.: Experience with a new contrast medium (Hypaque) for cerebral angiography. Radiology 67:537, 1956.
7. Broadbridge, A. T.: Hypaque in cerebral angiography. Brit. J. Radiol. 29:577, 1956.

Free amino acid content of cerebrospinal fluid in humans and dogs

John Logothetis, M.D.

In a previous communication[1] we have presented a chromatographic method and a survey analysis of free amino acids in the cerebrospinal fluid of normal human subjects and those with neurologic diseases. The present report includes a more detailed study of normal human subjects based upon a larger number of cases, as well as observations regarding the free amino acid content of cerebrospinal fluid in dogs.

Materials and methods

The cerebrospinal fluid of the human subjects was obtained from 52 individuals without apparent organic neurologic disorders, psychosis, or systemic disease. Thirty were cases undergoing spinal anesthesia for surgical removal of hypertrophic prostate, and the remaining 20 were patients with psychoneurotic disorders. All samples were collected by lumbar puncture and stored in the frozen state until analyzed. Laboratory studies for protein, sugar, cells and Wassermann reaction were carried out in most cases and were found to be within normal limits. In the entire group the age distribution was as follows: Fourteen patients were between ten and 40 years of age, 15 between 41 and 65 years of age, and 23 over age 65. Eleven of these subjects were females and 41 were males.

The cerebrospinal fluid of the dogs was obtained by puncture of the cisterna magna. A total of three healthy dogs were examined.

All spinal fluids were studied in duplicate or triplicate analyses using 1 ml. for each analysis. Use was made of two-dimensional chromatography using water saturated phenol and lutidine in mixture with ethanol and water (10:5:4). The quantitation of amino acid spots on the chromatogram was carried by direct photometry, using maximum color density and prepared calibration curves. The technical aspects of our method were presented elsewhere.[1]

Experimental results

The amino acids demonstrated in the human cerebrospinal fluid may be separated in three groups: 1 those demonstrated consistently (90 per cent and over), including alanine, aspartic acid, glycine, glutamine, serine, and valine; 2) those demonstrated inconsistently (less than 25 per cent), consisting of asparagine, alpha-aminobutyric acid, gamma-aminobutyric acid, proline, and phenylalanine; and 3) those appearing rather frequently (between 25 and 90 per cent) which include arginine, glutamic acid, lysine, leucine, tyrosine, and threonine. The presence of cystine could not be confirmed definitely, although spots were observed behaving as the cystine spots in control chromatographic studies. Figure 1 presents the total number of amino acids separated, as well as the incidence of occurence as determined by our method. The chromatographic appearance of these substances can be studied in figure 2. The quantitative values expressed in micrograms per ml. are presented in table 1.

It will be noted that the extreme minimal quantitative values of certain amino acids could not be determined sharply. This is due to the limitation in the usage of some calibration curves for small optical densities. Attempts were made to increase the amount of spinal fluid spotted in order to obtain denser spots on the paper. However, this was not

From the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.
This investigation aided by grant number B-1183 from the National Institute of Neurological Diseases and Blindness, National Institute of Health.

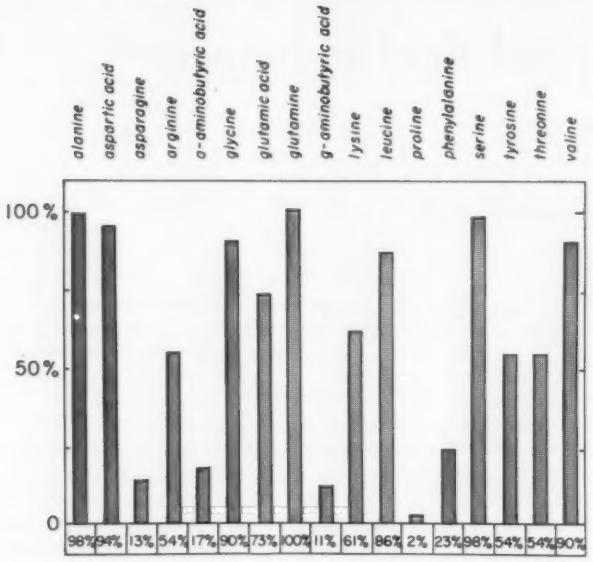


FIG. 1. The free amino acids and their incidence of occurrence in normal human cerebrospinal fluid.

found practical due to the increasing error in computing high optical density readings obtained from other amino acid spots on the chromatogram. It is apparent that a more accurate technic than the maximum color density photometry will be required to determine the minimal extreme values of these amino acids more exactly.

A breakdown of the normal values in relation to age groups indicated that there is no significant difference. There was, however, a tendency of glycine and serine to be higher in the young age group, whereas valine was lower.

The study of dog cerebrospinal fluids revealed about the same free amino acid distribution as in human beings. A representative chromatogram to compare with those obtained in humans is presented in figure 3. The quantitative results are tabulated in table 2. A com-

TABLE 1

NORMAL FREE AMINO ACID CONTENT OF HUMAN CEREBROSPINAL FLUID

(Summary of 52 Cases)

	Micrograms per ml. (mean + S.D. and range)
Alanine	1.5 ± 0.6 (0.3 — 1.8)
Aspartic acid	1.1 ± 0.6 (<0.3 — 2.2)
Arginine	1.6 ± 1.0 (<0.4 — 3.7)
Alpha-aminobutyric acid	0.2 ± 0.1 (<0.2 — 0.4)
Glycine	0.9 ± 0.4 (0.2 — 1.6)
Glutamic acid	0.9 ± 0.7 (0.2 — 2.5)
Gamma-aminobutyric acid	0.4 ± 0.2 (0.2 — 0.8)
Glutamine	>3.0 ± 1.0 (2.5 — 3.0+)
Lysine	1.7 ± 1.0 (0.2 — 2.9)
Leucine	1.4 ± 0.9 (0.6 — 3.0)
Phenylalanine	1.8 ± 1.1 (0.7 — 3.7)
Serine	2.2 ± 1.0 (0.5 — 3.0)
Threonine	1.2 ± 0.5 (0.2 — 2.3)
Tyrosine	1.6 ± 1.0 (<0.5 — 4.0)
Valine	1.2 ± 0.5 (0.2 — 3.1)

TABLE 2

NORMAL FREE AMINO ACID CONTENT OF DOG CEREBROSPINAL FLUID

	(Micrograms per ml.)		
	Dog 1	*Dog 2*	*Dog 3*
Alanine	1.8	1.8	1.8+
Aspartic acid	0.2	trace (<0.2)	1.9
Arginine	—	—	2.1
Alpha-aminobutyric acid	—	—	—
Glycine	0.4	0.4	0.8
Glutamic acid	trace (<0.2)	0.7	0.5
Glutanine	3.0+	3.0+	3.0+
Gamma-aminobutyric acid	0.6	0.6	—
Lysine	—	—	3.1
Leucine	1.9	1.4	2.1
Phenylalanine	1.1	—	1.3
Serine	2.1	1.6	2.7
Tyrosine	—	—	0.9
Threonine	1.4	1.2	1.7
Valine	0.9	0.6	1.3

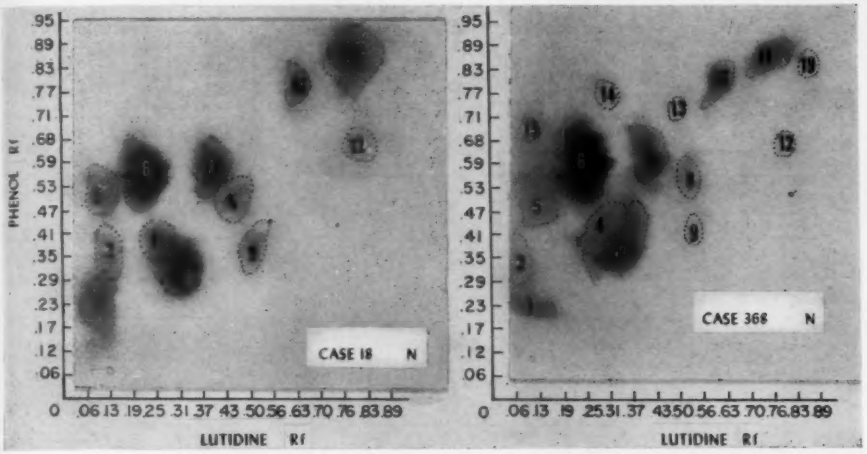


FIG. 2. The chromatographic appearance of the free amino acids in normal human cerebrospinal fluid. 1. aspartic acid; 2. glutamic acid; 3. serine; 4. glycine; 5. lysine; 6 glutamine; 7. alanine; 8. threonine; 9. taurine (added standard); 10. valine; 11. leucine; 12. tyrosine; 13. alpha-aminobutyric acid; 14. gamma-aminobutyric acid; 15. arginine.

parison of these values with the ones obtained in man reveals that several amino acids in dogs fall within the low human concentration ranges. This might be related to the different site of removal of the cerebrospinal fluid in dogs, that is, cisterna magna versus lumbar sac in man.

DISCUSSION

The literature regarding quantitaive analysis of cerebrospinal fluid from apparently normal individuals includes four important studies. Three of these studies have used paper chromatography and one column chromatography. The results of these studies as compared to our findings are demonstrated in table 3. It should be noted that values for alpha-aminobutyric acid and gamma-aminobutyric acid appear only in this study. Our results compare rather well with those of others.[2–4] Walker[2] used approximately the same chromatographic technic as in this work. Huisman[3] made use of quantitative column chromatography for this separation. Torre's work[4] was carried by paper chromatography and colorimetry. The values of Kemali[5] obtained by quantitative one dimensional chromatography were somewhat higher than those reported in the other studies.

Separation of the free amino acids in cerebrospinal fluid of dogs has not been reported previously in the literature. It is interesting that the amino acid content and values in dogs compare rather well with those of man.

SUMMARY

1. The free amino acid content of cerebrospinal fluid in man and dogs is presented,

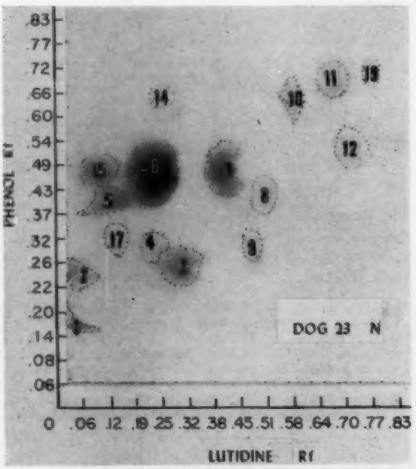


FIG. 3. The chromatographic appearance of the free amino acids in the cerebrospinal fluid of a healthy dog. 1. aspartic acid; 2. glutamic acid; 3. serine; 4. glycine; 5. lysine; 6. glutamine; 7. alanine; 8. threonine; 9. taurine (added standard); 10. valine; 11. leucine; 12, tyrosine; 14. gamma-aminobutyric acid: 15. arginine; 17. asparagine; 19. phenylalanine.

TABLE 3

COMPARATIVE STUDY OF THE FREE AMINO ACIDS IN THE NORMAL HUMAN CEREBROSPINAL FLUID*

	Kemali 1954 Paper chrom.	*Torre 1954 Paper chrom. 7 cases*	*Huisman 1955 Column chrom.*	*Walker 1955 Paper chrom. 26 cases*	*Author 1957 Paper chrom. 52 cases*
Alanine	8.4 (7.5 — 11.0)	0.8 (0.4 — 1.7)	1.5	1.1 ± 0.69	1.5 ± 0.6
Aspartic acid			1.0	0.4 ± 0.1	1.1 ± 0.6
Arginine		0.8 (0.5 — 1.25)	1.0		1.6 ± 1.0
Alpha-aminobutyric acid					0.2 ± 0.1
Cystine		2.1 (1.0 — 3.5)	0.5		
Glycine	4.8 (4.0 — 6.8)	1.1 (0.4 — 1.8)	1.0	1.0 ± 0.45	0.9 ± 0.4
Glutamic acid Glutamine	12.2 (10.5 — 13.1)	10.4 (5.0 — 17.6)	33.5	0.6 ± 0.3 7.1 ± 5.0	0.9 ± 0.7 >3.0 ± 1.0
Gamma-aminobutyric acid					0.4 ± 0.2
Histidine		2.2 (0.7 — 3.6)	0.5		
Lysine			2.0		1.7 ± 1.0
Leucine	2.4 (1.7 — 2.8)	1.1 (0.5 — 4.2)	0.5	1.4 ± 0.89	1.4 ± 0.9
Methionine			0.5		
Phenylalanine	1.8 (1.6 — 2.1)	0.9 (0.7 — 1.5)	1.5	2.1 ± 4.1	1.8 ± 1.1
Proline					
Serine			1.0	1.6 ± 0.7	2.2 ± 1.0
Tryptophan		2.6 (2.0 — 3.2)			
Threonine			3.0	1.3 ± 0.73	1.2 ± 0.5
Tyrosine	2.2 (1.9 — 2.5)	1.1 (1.0 — 9.0)	1.0	0.8 ± 0.32	1.6 ± 1.0
Valine	3.6 (3.0 — 4.2)	1.4 (0.5 — 4.1)	1.5	0.7 ± 0.52	1.2 ± 0.5

*The values are expressed in micrograms per ml. (means with S.D. or range of values are given as available).

based upon a quantitative chromatographic analysis.

2. The mean values of most amino acids range between 0.5 and 2.0 micrograms per ml. These results agree with those reported in the literature.

3. The content of the free amino acids in cerebrospinal fluid of dogs compares well with these of man. The concentrations for certain amino acids appear somewhat lower than in man.

REFERENCES

1. Logothetis, J.: A study of free amino acids in the human cerebrospinal fluid. Neurology 5:767, 1955.
2. Walker, B. S., Telles, N. C., and Pastore, E. J.: Amino acids of the cerebrospinal fluid, normal paper chromatographic pattern and its duplication in multiple sclerosis. Arch. Neurol. & Psychiat. 73:149, 1955.
3. Huisman, T. H.: Onderzoek Naar het Gehalte aan vershillende Aminozuren van de Liquor Cerebrospinalis. Ned. Tschr. Geneesk. 99:3337, 1955.
4. Torre, M., Scarzella, R., and Zanalda, A.: Ricerca cromatographica con dati quantitative degli aminoacidi liberi nel liquor di soggetti normali. Boll. Soc. It. Biol. Sper. 29:196, 1953.
5. Porcellati, G., and Kemali, D.: Il rapporto siero-liquor degli aminoacidi liberi. Giorn. biochim. Napoli 21-24, 488, 1954.

Neurology Volume 8 • Number 4

EDITORIAL

THE 1958 MEETING of the American Academy of Neurology closes the first ten years of active, fruitful growth and development of the organization. The membership has grown from the original 27 founding Fellows of the Academy ten years ago to well over 2,000 members today. In the first scientific program there were some 30 papers, and now the programs have increased so that more than a hundred papers are presented at the annual meeting. Early meetings of the Academy ran three days, and now six days is hardly time enough and it is found necessary to run concurrent sections.

Originally, communications between the members were literally by word of mouth at the annual meetings and on the few occasions when we met at other times. Now NEUROLOGY is our official communication, with scientific material within its regular pages and the news of the field of neurology carefully portrayed in the Newsletter. The officers of the Academy and the publisher, Mr. Louis M. Cohen, with courage and with some trepidation, launched volume 1 of the journal in 1950 with bimonthly issues. Within two years it expanded to become a monthly journal and now even the monthly issue is hard-pressed to publish all the scientific material.

The Academy has shown a dynamic approach to the field of neurology. This has been evidenced in the totality of its membership, so that from the first day of residency training in neurology until the last day of our lives we will still be members of the Academy. The special courses have done much in our self-education and have made Academy members well aware of the advances in our own field.

The development of special sections has allowed us to include within our membership basic scientists in the various areas of neurology and to have them participate with us in our meetings. This has resulted in a large increase in the material presented at meetings and has added a further load upon the publication facilities of the journal. It is for this reason that the special neurochemistry supplement appears with the April issue. These papers presented at the Section of Neurochemistry at the 1957 meeting in Boston are thus placed in the hands of the membership. The supplement is actually an extra dividend for Academy members and is a sign of the further growth of our organization.

How fitting it is that we meet in Philadelphia at the end of the first decade of our existence, with the founding of the Academy now a well-established fact and with its growth to full maturity assured. It is truly appropriate that we meet in this city where our own great nation was founded.

FRANCIS M. FORSTER, M.D.

CASE REPORT

Progressive dystrophy of the external eye muscles

Walter R. Kirschbaum, M.D. and John J. Holland, M.D.

INVOLVEMENT of the external eye muscles was first mentioned as an unusual late development in progressive muscular dystrophy at the turn of the last century.[1–4] It was known that myotonic dystrophy in the end stages interfered with the external eye movements. External ocular palsies, together with facial weakness and symmetric wasting of the shoulder girdles, arms, and leg muscles, were described as progressive myodystrophy in early papers.[5–8] However, primary chronic progressive external ophthalmoplegias limited to the eye muscles were, for the most part, considered neurogenic, as diseases of the oculomotor nuclei, in analogy to the well known degeneration of bulbar motor nuclei in progressive muscular atrophies. The authority of von Graefe[9] (1868), Moebius,[10] and the standard textbooks[11,12] supported this opinion.

A recent paper by Kiloh and Nevin[13] has changed this widely accepted conception; they proved the myopathic origin of five cases of progressive external ophthalmoplegia. These authors also reviewed the clinical reports of 99 similar cases published between 1868 and 1948. The clinical symptoms included stationary involvement of the eye muscles or extremely slow progress and only occasional spread to other muscles; the onset after birth or insidiously before 30 years of age; ptosis almost invariably present, frequently as a first sign; no periodicity and no remission, ending in total external ophthalmoplegia. About one half of the cases were familial and rarely were pupillary changes observed. In one quarter of the recorded cases various face, neck, and shoulder muscles were involved, and only 10 per cent presented additional disturbances of muscles supplied by the thoracic spinal segments. Furthermore, Kiloh and Nevin found no proof of pathologic changes in the oculomotor nuclei, roots, or nerves in the postmortem studies.[14–16] Instead, the muscle biopsies of Kiloh and Nevin's cases, as well as earlier histologic studies of the extraocular muscles, revealed a chronic dystrophic myodegeneration. Electrodiagnostic and electromyographic studies of the external eye muscles were of diagnostic value as long as the myodegeneration was not too far advanced. A neurogenic muscular atrophy should lead myographically to a discharge of fewer motor units but with normal amplitude of those remaining, while the dystrophic muscle fibers produce low amplitude potentials, though their recruitment might remain abundant.[17]

The case to be presented was diagnosed before and reevaluated after the publication of Kiloh and Nevin's paper.

CASE REPORT

A 35 year old white male with negative family history had developed in the early teens a bilateral ptosis of the eyelids, for which surgery was performed at age 16 with good results on the left and poor results on the right eye. He was a mentally slow, passive individual who completed public school and did odd jobs before induction into the Army in 1941. Since then he complained of headaches, double vision, and difficulty in moving the eyes. After a long stay in several Army hospitals, he was discharged (1944) with the diagnosis of progressive external ophthalmoplegia.

From the department of neurology and psychiatry, Northwestern University Medical School, Chicago, and the neurologic and ophthalmologic services, Veterans Administration Hospital, Hines, Illinois.

Read to the Chicago Neurological Society, May 21, 1957.

He was admitted to the neurology service of the Veterans Administration Hospital, Hines, Illinois, September 8, 1948 with ptosis of both eyelids, marked limitation of the eye movements, headaches, and visual disturbances. There were almost complete bilateral fixation of gaze, slight movement toward the left, and a flicker of motion toward the right and downward. The right palpebral fissure measured 5 mm., the left 8 mm. Pupils reacted to light and accommodation normally; the peripheral visual fields were normal. Visual acuity—right 20/30; left 20/50. A Prostigmin test for myasthenia gravis was negative, as were the spinal fluid examinations and the electroencephalogram. There were no other neurologic findings. On September 30, 1948 he was discharged with a diagnosis of bilateral progressive external ophthalmoplegia, with involvement of the third, fourth, and sixth cranial nerves.

On July 11, 1955 he entered the ophthalmologic service of the same hospital with corneal ulcer of the left eye, blepharitis, keratitis, and ophthalmoplegia. A corneal ulceration resulted from exposure and a lack of Bell's phenomenon after surgery for ptosis. The neurologic reexamination showed a slight weakness of the anterior cervical muscles on forward flexion of the head and a nasal sound in his speech, in addition to the previous findings. Electrodiagnostic and electromyographic examinations of the right and left palatal muscles and of the tongue showed normal tracings and no fibrillary activities. Electromyographic studies of the left medial and lateral ocular rectus showed no fibrillary activity at rest; during attempted voluntary motion some activity of very low amplitude occurred, with occasional bursts up to 50 microvolts and many action potentials with durations of 3 to 4 milliseconds. Electromyography of the right medial, superior, and inferior rectus showed no activity during rest or attempted voluntary motion. Some activity of the right lateral rectus was present, with potentials of about 20 microvolts and high frequency, each less than 1 milliseconds duration. These findings were not conclusive.

A biopsy from the midportion of the left lateral rectus muscle on December 13, 1955 was fixed in Zenker fluid and stained with hematoxylin and eosin, van Gieson's, and Bodian's methods. It showed advanced degeneration, swelling, dissolution, fragmentation, and shrinkage of the muscle fibers, proliferation of the sarcolemmal nuclei, formation of nuclear bags, and thickened endomysial and perimysial fibrous sheaths. Many nerve fibers were preserved, some of them definitely motor, as evidenced by well structured motor end-plates on degenerating muscle fibers. Some of the motor nerve endings were sprouting hypolemmally to form secondary telodendria in attempts of reinnervation (figures 1 and 2).

On reexamination May 21, 1957 the patient's condition was unchanged. The external ophthalmoplegia remained as complete as in 1955. There were normal phonation and no weakness of the muscles of the face and neck.

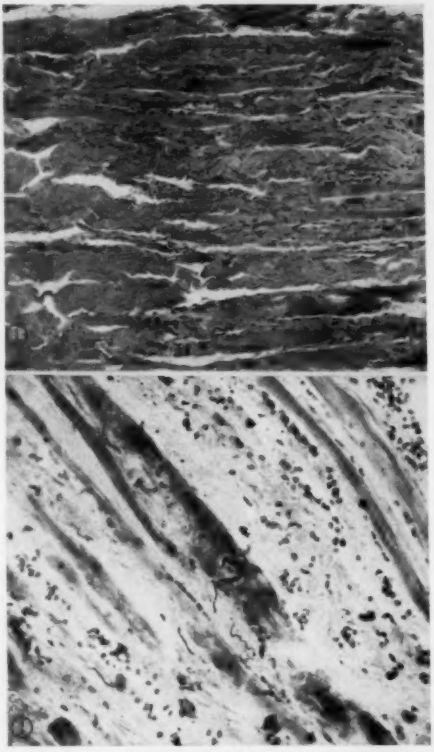


FIG. 1. Muscle fibers in various states of degeneration, swelling, reduction in size, and fragmentation with rows and clusters of sarcolemmal nuclei. Heavy layers of endomysial fibrous tissue abound and stretch between the few remaining muscle fibers (hematoxylin, van Gieson's method).

FIG. 2. A swollen and severely degenerated muscle fiber containing elongated, deeper staining, and light, almost transparent, vesicular nuclei. The end portion of the entering motor fiber is well preserved, though thickened, at the sarcoplasmatic junction and forms secondary outgrowths, telodendria. A clear space surrounds the neurofibrillar termination of the motor axon (Silver impregnation, Bodian's method).

DISCUSSION

This case presents the ocular type of progressive muscular dystrophy. A fluctuating weakness of the neck and pharyngeal muscles may point to symptoms seen with the facioscapulohumeral subgroup of Landouzy-Déjerine. Hypoplasia and bilateral weakness of the levator palpebrae muscles precedes for many years the palsies of the other eye muscles. The preservation of the motor end-plates in the

degenerated muscle fibers is evidence against a congenital malformation of the nuclear centers or a nuclear amyotrophy. Histopathologically, it is not the denervatory but the mere degenerative type of reaction of the muscle fibers.[18] Since postmortem examinations of the ocular nuclei are void of significant changes, electromyographic studies favor myodystrophy. Without disregard for the occurrence of chronic progressive nuclear palsies of the eye muscles due to developmental, toxic-degenerative, vascular, or infectious conditions in syringobulbia, multiple sclerosis, diabetes, Grave's disease, neurosyphilis, and so on, the vast majority of cases have no central nuclear but a myodegenerative pathogenesis.

SUMMARY

A 35 year old white male with negative family history manifested bilateral ptosis of the eyelids in his early teens. A complete external ophthalmoplegia developed in the following years and has remained stationary since. The case represents the ocular type of progressive muscular dystrophy. A nuclear amyotrophy was definitely ruled out by the preservation of the motor end-plates in the severely degenerated fibers of the external eye muscle, as demonstrated in biopsy studies. Electromyographic examinations were not conclusive due to the far advanced myodegeneration. Muscle biopsies from the midportion of the eye muscle established the diagnosis.

REFERENCES

1. Landouzy, L., and Dejerine, I.: De la myopathie atrophique progressive (myopathie héréditarie debutant, dans l' enfance, par la face, sans alterations du systeme nerveux). Compt. rend. Acad. sc. 98:53, 1884.
2. Bouveret, L.: Deux cas de myopathie atrophique progressive. Lyon méd. 80:148, 1895.
3. Sano, F.: Amyotrophic progressive primitive. Ann. Soc. méd. d'Anvers, 1897; Rev. neurol. 9:446, 1901.
4. Marie, P.: Sur une forme de myopathie progressive primitive avec ptosis bilatéral et participation des muscles masticateurs. Rev. neurol. 9:446, 1901.
5. Hutchinson, I.: On ophthalmoplegia externa or symmetrical immobility (partial) of the eyes with ptosis. Tr. Roy. Med. Chir. Soc. London 62:307, 1879.
6. Seeligmüller, V.: Ein Fall von chronischer progressiver Polioencephalitis. Zentralbl. Neurol. 8:153, 1889.
7. Winkle, C., and Van der Weyde, A. J.: Primaire myopathie gekombineerd met "ophthalmoplegia progressiva superior." Nederl. tijdschr. geneesk. 25:69, 1889.
8. Fuchs, E.: Ueber isolierte doppelseitige Ptosis. Arch. Ophthalmologie 36:234, 1890.
9. Von Graefe, A.: Doppelseitige Ophthalmoplegie; Medizin. Gesellschaft 2:19, 1868; Klin. Wchnschr. 5: 127, 1868.
10. Moebius, P. J.: Ueber die hereditären Nervenkrankheiten. Die hereditäre oder degenerative Muskelatrophie. Sammlung Klinischer Vorläge (Innere Medizin No. 57). 2:1505, 1879.
11. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges. Vol. 1:212, 1899. I. F. Bergmann Co., Wiesbaden.
12. Duke-Elder, Sir W.: Textbook of Ophthalmology. 1949, Vol. 4, p. 4094. C. V. Mosby Co., St. Louis.
13. Kiloh, L. G., and Nevin, S.: Progressive dystrophy of the external ocular muscles (ocular myopathy). Brain 74:115, 1951.
14. Langden, H. M., and Cadwalader, W. B.: Chronic progressive external ophthalmoplegia. Brain 51:321, 1928.
15. Jedlowski, P.: (cited by Kiloh and Nevin) Riv. oto-neuro-oftal. 20:203, 1943.
16. Giardini, A.: Considerazioni su una forma "pura" di oftalmoplegia externa nucleare cronica progressiva. Riv. oto-neuro-oftal. 23:181, 1948.
17. Breinin, G. H.: Electromyography, a tool in ocular and neurologic diagnosis. II. Muscle palsies. Arch. Ophth. 57:165, 1957.
18. Kirschbaum, W. R.: Histological studies of muscle tissue in neuro-muscular diseases. J. Neuropath. & Exper. Neurol. 11:373, 1952.

■ Spinal congestion, or plethora spinalis, is not less definite in its history than myelitis or spinal meningitis; neither is it of less practical interest. In the sequel, indeed, it may appear, not only that spinal congestion is fully entitled to the place which has been assigned to it in the catalogue of diseases, but also that it really comprehends more than one spinal disorder which is now known under a different name.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

CASE REPORT

Paralysis of the dorsal interosseous nerve not due to direct trauma

A case showing spontaneous recovery

Francis Kruse, Jr., M.D.

Paralysis of the dorsal interosseous (deep radial) nerve resulting from direct trauma to the nerve has been reported as due to a wide variety of injuries. These have included gunshot wounds,[1] a circular saw wound,[2] an elbow sprain with subsequent pressure during sleep,[3] and a case in which the nerve was directly involved in a tumor near the elbow.[4] Occupationally, it has been noted to occur in bricklayers as the result of pressure from bricks carried on the forearm. A certain number of cases have accumulated in the literature in whom there is no history of direct trauma but, supposedly, a relationship to frequent repetitive movements of pronation and supination, as in the case of an orchestra leader,[5] a pianist,[4] and a corsetiere.[6] A few other cases have also been reported in whom there was neither direct trauma nor apparent occupational relationship.[4,7] Recovery is rare, and a general pessimism has been noted.[6,8]

A variety of speculations have been advanced to explain the syndrome of paralysis and subsequent atrophy of the muscles innervated by the dorsal interosseous nerve. Guillain and Courtellement[5] indicated that the cause might lie in chronic trauma to the nerve caused by frequent and prolonged pronation and supination, since the nerve passes through the substance of the supinator brevis muscle. Woltman and Learmonth[4] explained the paralysis on the basis of an anomalous course of the nerve. The normal course of the dorsal interosseous nerve is through the substance of the supinator brevis muscle, where two branches of distribution occur at the lower border of the muscle. The first of these innervates the extensor digitorum communis, extensor digiti quinti proprius, and the extensor carpi ulnaris. The other supplies the abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, and the extensor indicis proprius.

Harburger[9] described an anomalous course in which the branch to the deep group of muscles is divided, with one twig appearing in the usual situation and preceding to supply the extensor pollicis longus and extensor indicis proprius. The other passes through the substance of the supinator brevis above its lower border and is distributed to the abductor pollicis longus, extensor pollicis brevis, and to a special extensor proprius digiti medii. Luschka and Krause[10] described an anomalous course in which the branch to the deep group of muscles passes superficial to the supinator brevis. In one of the cases of Woltman and Learmonth which was operated upon, the entire nerve was found to be superficial to the muscle.[4] A strip of the extensor aponeurosis was excised over the course of the nerve without clinical improvement. It was felt that the anomaly might be the basis of the disability.

Weinberger[6] believed the idiopathic palsies to be due to proximity of the nerve to bursae of the upper forearm, noting that the nerve skirts lateral and posterior to the bicipitoradial and interosseous bursae of the elbow. He noted that there is evidence to suggest that bursitis can produce alterations of function and neuritic signs in a nerve adjacent to an inflamed bursa; in 12 published cases there were reports of pain in the arm, and in six of these there was noted to be tenderness on examination. He emphasized that the point of

From the neurology section, 2349th USAF Hospital, Parks Air Force Base, California.
Present address: Armed Forces Institute of Pathology, Washington, D. C.

tenderness on deep palpation is over the area of the bicipitoradial and interosseous bursae.

In most cases paralysis of the dorsal interosseous nerve has been permanent. However, Weinberger cited a case in whom surgery revealed "a small bursal cystic sac connected to the bicipitoradial bursa. The median nerve invested the anterior surface and the posterior interosseous nerve was closely applied to and compressed by the posterior wall." This case is said to have recovered subsequently. Weinberger has urged an operative approach to the nerve in the region of the bursae for relief of the paralysis.

In view of the apparent rarity of recovery, the following case in whom there was complete recovery is presented.

CASE REPORT

A 38 year old white female was seen in the neurology out-patient clinic with the initial complaint of weakness of her right hand. She had gone swimming on July 4, 1955 and had been swimming actively for several hours. Shortly after arriving home from the swimming pool she noted pain and stiffness in her right elbow. She went to bed thinking the pain would be relieved by sleep, but awoke the next morning with even more pain and stiffness in the elbow. Later that day she noted some slight weakness in extending the fingers of the right hand, and the following day there was marked weakness. On examination, four days following the onset of pain in the elbow, she was unable to extend the fingers of her left hand at the carpal phalangeal junction. There was also slight weakness of extension of the hand at the wrist and abduction of the thumb was moderately impaired.

An electromyogram was first performed on August 8, 1955. The extensor digitorum communis showed complete electrical silence at rest. On voluntary contraction there were found to be a few simple motor units, but no complete motor units or fibrillation potentials were seen. There were occasional simple motor units in the extensor indicis proprius, these being much fewer than are normally seen. Examination of the brachioradialis revealed electrical silence at rest and on maximal contraction there was a normal interference pattern. An electromyogram obtained on September 19, 1955 revealed many fibrillation potentials and positive sharp waves in all areas of the extensor digitorum communis sampled. On voluntary contraction there was no further local electrical activity. In the extensor carpi ulnaris there was electrical silence at rest and simple motor units on voluntary contraction.

Following her initial examination, the patient was placed on a treatment regime consisting of galvanic stimulation of the affected muscle groups, and attempted re-education of the affected musculature was begun. On January 11, 1956 some apparent return in the extensor digitorum communis was noted. By February 3, 1956 this return was marked. An electromyogram obtained at this time showed a pattern consistent with re-innervation. Progress was steady and considerable until it was felt that complete return of function had been achieved by the end of March 1956. Neurologic examination throughout the course of this patient's illness was negative, except for the weakness of the muscles innervated by the dorsal interosseous nerve. No sensory loss was found at any time.

DISCUSSION

In the case presented, it is noteworthy that paralysis occurred subsequent to the onset of elbow pain following severe and unaccustomed use of the arm. Pain on pressure over the position of the bicipitoradial and interosseous bursae of the elbow was noted. This finding corresponds to the possibility of bursitis of these bursae involving the contiguous dorsal interosseous nerve.[6]

The case is apparently unusual, in that complete recovery occurred after nine months. This would indicate the changes in the nerve are not as irreparable as thought previously. Electromyographic findings may guide therapy of such palsies, with operative intervention being reserved only for those cases which might show complete denervation after a sufficient period of time has elapsed.

REFERENCES

1. Roussy, G., and Branche, J.: Deux cas de paralysies dissociees de la branche posterieure du radial a type de pseudo-griffe cubitale. Rev. neurol. 32:312, 1917.
2. Mowell, J. W.: Posterior interosseous nerve injury. Internat. Clin. 2:188, 1921.
3. Grigoresco, D., and Iordanesco, C.: Un cas rare de paralysie partielle du nerf radial. Rev. neurol. 2: 102, 1931.
4. Woltman, H. W., and Learmonth, J. R.: Progressive paralysis of the nervous interosseous dorsalis. Brain 57:25, 1934.
5. Guillain, Georges, and Courtellement: L'action du muscle court supinateur dans la paralysie du nerf radiol. Pathogenie d'une paralysie radiale incomplete chez un chef d'orchestre. Presse méd. 1:50, 1905.
6. Weinberger, L. M.: Non-traumatic paralysis of the dorsal interosseous nerve. Surg., Gynec. & Obst. 69: 358, 1939.
7. Jumentie, M. J.: Fausse griffe cubitale par lesion dissociee du nerf radial. Rev. neurol. 37:756, 1921.
8. Hobhouse, Neil, and Heald, C. B.: A case of posterior interosseous paralysis. Brit. M. J. 1:841, 1936.
9. Harburger, Adrien: Anomalie de division de la branch posterieure du nerf radial extenseur propre du medius. Bull. Soc. Anat. de Paris 94:236, 1924.
10. Luschka and Krause, as quoted by Hovelacque, A.: Anatomie des Nerfs Craniens et Rachidiens et du Systeme Grand Sympathique. Paris, G. Dorn et Cie., 1927.

Neurology

BOOK REVIEWS

Modern Trends in Neurology

(Second Series) Edited by Denis Williams, C.B.E., M.D., D.Sc., F.R.C.P. 1957. New York: Paul B. Hoeber, Inc. 350 pages. $13.50.

THIS VOLUME, the second on the subject, is a sequel to one edited by Dr. Anthony Feiling in 1951, but there is little overlap of subjects or subject matter. The various contributors were chosen because of their known interests, and Dr. Williams instructed each to assume a high level of knowledge in his readers, to review current work critically and concisely, and to follow the trend of his work as far into the future as scientific propriety would allow. Thus, judging alone from the selection of authors and the timeliness and scope of subject matter, one may conclude that this volume is a most comprehensive review of current advances in neurology.

The standard of the contributions is so high that it is difficult to select individual articles for review. One would be remiss, however, if he did not mention specifically the discussion of metabolic disturbances affecting the cerebrum by Dr. John N. Cumings, the review of his own important and revolutionary investigations on the formation and absorption of cerebrospinal fluid by Dr. William H. Sweet, the critical analysis of electromyography by Dr. R. W. Gilliatt, the review of etiologic factors and pathology of cerebral atherosclerosis by Professor T. Crawford, the consideration of intracranial angiomas by Dr. J. Hamilton Patterson and of occlusion of the internal carotid arteries by Sir Charles Symonds, the presentation of current concepts of intracranial hypertension by Dr. John Foley and of primary muscle disease by Professor F. J. Nattrass, and a timely review of cervical spondylosis by Mr. Valentine Logue. There are two sections which are of special interest. One of these is an appraisal of temporal lobe epilepsy, consisting of a description of the pathology of the hippocampal lesions by Professor A. Meyer and a discussion of the clinical and pathophysiologic aspects by Dr. Williams himself. The other is two chapters by Professor Charles E. Lumsden on the chemistry of myelin and cell structure and physiology in relation to myelin.

The above constitute but a portion of the book, but they indicate the choice of subjects and the caliber of the contributors. The volume is not only a noteworthy review of present trends in neurology, covering the basic sciences as well as the clinical aspects, but it also gives insight into current and future developments in research. One who wishes to keep abreast of these fields and have an authoritative reference in guiding his own reading and investigations would be rewarded by having this book available.

R. N. DE J.

Atlas of Neuropathology

Nathan Malamud, M.D., 1957. Berkeley and Los Angeles: University of California Press. 486 pages. $20.00.

PRECISE and detailed knowledge of the gross and microscopic changes in the nervous system is a necessary prerequisite to the understanding of its diseases. Dr. Malamud, associate clinical professor of psychiatry and neuropathology at the University of California Medical School in San Francisco and neuropathologist at the Langley Porter Clinic, has, in this book, used a visual approach to the problem that is not found in general textbooks of neuropathology. He has provided an atlas that should prove to be of outstanding value to workers in the fields of neurology, neurosurgery, psychiatry, and pathology.

Following a rather short introduction dealing with cytology and cellular pathology, the author has discussed in some detail the more important inflammatory, toxic and nutritional, demyelinating, vascular, traumatic, degenerative, neoplastic, and developmental disorders of the nervous system, choosing his material from some 5,000 specimens examined personally. He has attempted to illustrate each of these as comprehensively as possible. Nearly equal space has been given to each category, but special attention has been paid to such neglected conditions as the heredodegenerative disorders and those pertaining to geriatrics, cerebral palsy, and mental deficiency. The case presentation method has been used wherever possible to afford a correlation between clinical syndromes and pathologic alterations.

The book is beautifully printed and illustrated, and an excellent choice of case material is used for both cases and specimens. The gross material is well dissected out and photographed, and the microscopic sections, some in color, are superb. All illustrations are very well reproduced, so well, in fact, that they can easily be projected or even rephotographed. This book is not, and does not pretend to be, a complete text of neuropathology. However, it is very comprehensible, and can serve both as a reference work and as a guide to the study of neuropathology. This is such an important book that it should be available to all practitioners and students of neurology.

R. N. DE J.

Ultrastructure and Cellular Chemistry of Neural Tissue

Edited by Heinrich Waelsch, M.D. Volume II of Progress in Neurobiology, *Series editors Saul R. Korey and John I. Nurnberger. 1957. Paul B. Hoeber, Inc., New York, N.Y. 249 pages. $7.50.*

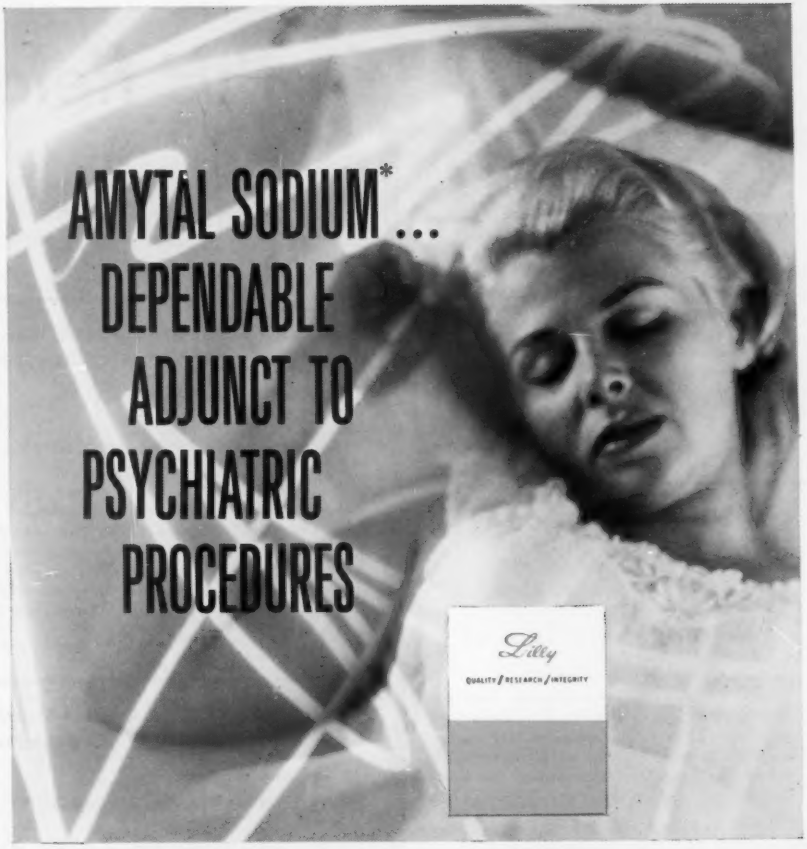
THIS PUBLICATION is the second in a series of symposia dealing with recent advances in the investigation of the nervous system. It presents many of the newer methods employed in the physical and chemical study of the minute organization of neural tissue. The material contained offers a broad spectrum of interest to those conducting research in all neurologic fields. Papers are sufficiently detailed to describe methodology and contain data adequate to demonstrate the value of these methods.

The initial sections deal with electron microscopic investigations of the ultrastructure of the nerve, synapse, voluntary muscle fiber, and neurohypophysis by J. D. Robertson and by S. L. Palay. The following papers are predominantly concerned with nervous system chemistry on a cellular level. The technics and results of analysis of the single nerve fiber are lucidly described by Oliver Lowry. Histochemical studies of normal and pathologic tissue are well represented in sections covering nervous system lipids, esterases, and proteolytic and oxidative enzymes. The problems pertaining to cell density as a reference in neurochemical studies are presented by J. I. Nurnberger and M. W. Gordon, together with a description of their technic for the enumeration of cells. The effects of barbiturates and chlorpromazine on cerebral phosphorus metabolism are reported by J. A. Bain and M. Berger and on tissue culture by R. S. Geiger. The technic of television scanning microspectrophotometry as reported by C. N. Loeser is of possible import in neurologic research, but has not yet been applied extensively to neural tissue.

The figures and plates are complete and well selected. Reproduction, particularly of electron micrographs, is of uniformly high quality.

The selection, lucidity, and completeness of presentation make this book a valuable source of reference to the neurologic investigator.

M. M. C.



Versatile, moderately long-acting hypnotic

- restores normal sleep cycle in acute excitement
- provides prompt, prolonged narcosis in psychiatric patients
- aids in differential diagnosis between functional and organic disease
- useful in psychiatric evaluation by narcoanalysis

Available in 1 and 3-gr. pulvules, and ampoules ranging from 1 gr. to 15 1/2 grs.

*'Amytal Sodium' (Amobarbital Sodium, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Lilly
POLIO VACCINE
820000

5 NEW BOOKS *in this field*

of special interest to you!

EPILEPSY HANDBOOK

By Frederic A. Gibbs and Frederick W. Stamps, Univ. Ill.

A brief but comprehensible account of what epilepsy is, the forms it takes and how it can be treated. Written simply yet authoritative and scientifically accurate. Sets out *essential facts* about convulsive and masquerading forms of epilepsy with detailed practical information on: selection of drugs, dosage, medical management of difficult cases and indications for surgery.

Pub. '58, 96 pp., 9 il., Cloth, $4.25

CLINICAL NEUROLOGY, NEUROANATOMY AND NEUROPHYSIOLOGY

By Louis Hausman, Cornell Univ.

From the *clinical perspective of the patient at the bedside*, it is based on and represents an elaboration of the method originally described by Adolf Meyer. All three disciplines are integrated into one unit. Each is considered in terms of the other two. In addition, a method of reconstructing the brain is presented.

Pub. Spring '58, 500 pp., 10 plates

THE MORAL THEORY OF BEHAVIOR (Third Printing)

By Frank R. Barta, Omaha

"A New Answer to the Enigma of Mental Illness" is the sub-title of this challenging little book which offers a new theory of behavior based on Aristotelian and Thomistic principles of Philosophy and psychology. In reviewing the book, the Digest of Neurology and Psychiatry said "it has a religious emphasis for which there is ample room in the field of psychiatry."

Pub. '57, 45 pp., 3 il., $2.00

ELECTRONIC INSTRUMENTATION FOR THE BEHAVIORAL SCIENCES

By Clinton C. Brown and Rayford T. Saucer, Veterans Adm. Hosp., Perry Point, Md.

By presenting electronic theory, circuit design and a wide variety of instrumentation techniques, this book provides the features of both a text and a handbook. For research investigators in experimental psychiatry, psychophysiology, physiology and other fields where electronic instrumentation is employed for stimulation or measurement of response processes.

Pub. '58, 176 pp., 73 il., $5.50

THE HANGOVER: A Critical Study of the Psychodynamics of Alcoholism

By Benjamin Karpman, St. Elizabeth's Hosp., Washington, D.C.

A *frank* and *penetrating* study of the lives of seven men and seven women alcoholics in which the "hangover" is shown to be symptomatic of the specific underlying personality disorders leading to alcoholism. Contributes to a new and deeper understanding of emotional and personality factors leading to alcoholism.

Pub. '57, 360 pp., 16 il., Cloth, $9.50

CHARLES C THOMAS • PUBLISHER

301 - 327 East Lawrence Avenue

Springfield, Illinois

IPRONIAZID

the psychic energizer
is available only as

MARSILID

Roche

Marsilid® Phosphate
brand of iproniazid phosphate

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley 10, New Jersey

ROCHE®

Original Research in
Medicine and Chemistry

Two days ago,
he was manic,
hostile,
aggressive

. . . today he is calm, sociable,
easy to manage

SPARINE is established as an effective drug for the management of patients with acute or chronic mental disturbances. It rapidly subdues excitation and facilitates patient contact.

SPARINE provides prompt control by intravenous administration and effective maintenance by the intramuscular or oral route. It is well-tolerated by all routes of administration. It has caused no liver damage, no parkinsonian-like syndrome, and but rare instances of blood dyscrasia or seizures.

Sparine® INJECTION TABLETS SYRUP

HYDROCHLORIDE Promazine Hydrochloride

A Wyeth normotropic drug for nearly every patient under stress

EQUANIL® Meprobamate
PHENERGAN® HCl Promethazine HCl
SPARINE HCl Promazine HCl

Wyeth®
Philadelphia 1, Pa.

Products and Services

The information below was supplied by the manufacturers

THREE NARCOTICS NOW AVAILABLE IN TUBEX CLOSED-SYSTEM INJECTABLES

Three frequently used narcotics have been added by Wyeth Laboratories, Radnor, Pennsylvania, to the Tubex line of closed-system medications for injections. Codeine phosphate, meperidine hydrochloride, and morphine sulfate are now available in 1 cc. doses.

For the physician and the hospital staff, the Tubex system provides an unbreakable and permanent metal syringe with disposable medication-containing cartridges. A sterile needle, protected by a guard, is affixed to each container. The cartridge-needle unit is used only once and discarded. This system eliminates sterilization, needle-sharpening, syringe breakage, and other costly, time-consuming factors. Tubex insures accurate dosage.

BALDPATE, Inc.

Geo. Fleetwood 2-2131 **Georgetown, Mass.**

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Definitive psychotherapy, somatic therapies, pharmacotherapy, milieu-therapy under direction of trained occupational and recreational therapists.

HARRY C. SOLOMON, M.D.
Consulting Psychiatrist

GEORGE M. SCHLOMER, M.D.
Medical Director

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
John D. Marshall, Jr., M.D.
Peter P. Barbara, Ph.D.
Heide F. and Samuel Bernard, Administration

New York Office: 33 East 74th St. LEhigh 5-5155

for those with

PARKINSONISM

"... in our experience procyclidine (Kemadrin) proved a worthy addition to the therapy of parkinsonism, because it afforded relief to many patients who had failed to respond to other drugs. It exerts an action against all symptoms of parkinsonism ... hence it may be employed as the basic drug in commencing treatment with new cases."

Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

"... in our series of 30 severe Parkinsonism sufferers, 21 obtained moderate to good relief with the use of this new agent, Kemadrin, in combination with other drugs."

Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

Smoother activity,
and *brighter expression*

with 'KEMADRIN'®

Also indicated for the treatment of drug-induced symptoms resembling parkinsonism, developing during treatment of mental patients.

'KEMADRIN' brand Procyclidine Hydrochloride
Tablets of 5 mg., scored. Bottles of 100 and 1,000.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

MODEL D
ELECTROENCEPHALOGRAPH

The improved Model D Electroencephalograph presents all of the latest advances in component reliability and manufacturing techniques, retaining the advantages of ease of operation and maintenance built into the instrument during over ten years of experience in manufacture and application.

New components, such as strain gage amplifiers, D. C. channels, etc. are available. Special amplifiers can be designed and furnished upon submission of specifications. All of these units are arranged for easy plug-in installation in the standard console.

write for descriptive literature and prices on:

ELECTROMYOGRAPHS
ELECTROENCEPHALOGRAPHS
STRAIN GAGE AMPLIFIERS
RECORDER PAPER
ELECTRODES
SHOCK THERAPY EQUIPMENT

MEDCRAFT ELECTRONIC CORP.

designers and manufacturers of diagnostic and therapeutic equipment for the medical profession

426 GREAT EAST NECK ROAD, BABYLON, N.Y.

TEL. MOHAWK 9-2837 ADDRESS MAIL TO BOX 1006, BABYLON, N.Y.

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

Francis M. Forster, President
Augustus S. Rose, President-Elect
A. L. Sahs, Vice-President
Joseph M. Foley, Secretary
Charles Van Buskirk, Treasurer

APRIL 1958

Development of Soviet Neurology Under the Sixth Five-Year Plan

At the Twentieth Congress of the Communist Party of the Soviet Union on the Sixth Five-Year Plan (1956-1960) for the development of the national economy, a program was structured for attaining the highest possible activation of medical science, and for concentrating the forces of Soviet scientists on research for new methods of prevention and treatment of disease. According to a 12-page report entitled "Problems of Clinical Neurology in the SIXTH FIVE-YEAR PLAN,"[1] clinical neurology is essential to the development of Soviet public health and medical science. The author, Professor N. I. Grashchenkov of Moscow, was a vice-president representing the USSR at the First International Congress of Neurological Sciences, Brussels (July 21-28, 1957).... In his report, Grashchenkov maintains that clinical neurology represents the action center of the entire organism and, therefore, progress made in this field contributes to progress in all divisions of clinical medicine and biology.

Theoretical Substratum of Clinical Neurology

According to the Grashchenkov report, the theoretical basis of modern clinical neurology is based on recent advances in physiology and pathophysiology, and particularly in biochemistry and biophysics as they relate to the nervous system; also emphasized are new theories in and for the development of neurologic instrumentation. He underscores the application of the principles of atomic energy to neurologic problems, the introduction of histochemical technics, and the new advances made in studies on fine nervous structure by phase contrast and electron microscopy. "Indeed, it may be said" writes Grashchenkov, "that we are living in a century of great speeds, small magnitudes, and objective recordings of the finest microscopic and even ultramicroscopic phenomena in the structure and function of the nervous system. Our technical armament and the theoretical level of clinical neurology are thus defined."

Cerebrovascular Disease is Primary Research Target

According to the report, cerebrovascular disease is the major research challenge facing Soviet neurologists. He divides these conditions broadly, 1) irreversible lesions, and 2) the reversible dynamic disorders of the cerebral circulation. The

[1] *Zhurnal nevropatologii i psikhiatrii imeni S. S. Korsakova.* Journal of Neuropathology and Psychiatry imeni S. S. Korsakova, Vol. LVI, No. 10, October 1956, Moscow, pages 765-777.

latter disorders usually arise against a background of hypertensive disease of neurologic origin, and are associated with varying degrees of consciousness, inconstant reflex changes, pupillary changes, and manifest sympathetic vascular disturbances. These conditions, according to Grashchenkov, can be checked in the USSR, if diagnosed early, thanks to the work of Ye. M. Boyeva. Investigations have shown that they result from spastic and dilatation phenomena of the cerebral vessels, coupled with a focal or generalized edema of the brain parenchyma. But he adds, "the problems of the dynamic disorders of the cerebral circulation still cannot be considered completely solved."... Regarding the irreversible lesions, the report recommends further testing of anticoagulants as preventatives or treatment for thrombosis, and the Frakshteyn restorative technics for neurologic residuals, if established. These rehabilitation procedures, reportedly, have been developed from sound pathophysiologic studies, and from studies of central regulation of cervical, tonic, and position reflexes at different levels of the brainstem, subcortex, and cortex.

Other Disease Targets in Neurologic Research The report stresses the important role of neurologists in relation to infectious disorders of the nervous system. Clinical neurologists should be trained in the essentials of microbiology, but, even more important, they must study and develop practical measures with respect to the epidemiologic, pathologic, and other scientific aspects of neuroinfections. Much is made of the sequelae of neuroinfections, and of the toxi-infectious influences of recurrences of common systemic infections, which may disturb brainstem mechanisms and brain metabolism, giving rise to subtle neurologic syndromes. For these conditions, Grashchenkov states, "clinical neurologists must develop a pathogenic therapy apart from etiologic therapy."... Answers to the problems posed by degenerative diseases of the nervous system await further advances in our knowledge of ionic-metabolic disturbances, either ingrained or acquired, and in the development of new biochemical and biophysical technics. Multiple sclerosis and amyotrophic lateral sclerosis are not included in the degenerative group because of their possible virus etiology, a concept which is still preserved due to the investigations of Margulis, Shubladze, and Solov'yeva.... Throughout the report, urgency is stressed on the development of detecting factors and antidotes against the noxious effects of ionizing radiations.

Neurologic and Neurosurgical Team Approach The Soviet program calls for a team approach by neurologists and neurosurgeons for attacking particular problems, especially for the management of open and closed head injuries, brain tumors, and types of focal epilepsy where surgical intervention is being developed in combination with anticonvulsive therapy.... The importance of a trend toward ever wider

interdisciplinary collaboration in attacking individual neurologic problems is to be encouraged and regarded as a ramification of Pavlov's concepts of "nervism" through all fields of clinical and theoretical medicine. As a trend to this kind of interdisciplinary collaboration, Grashchenkov sites the psychoprophylactic trend in the anesthesia of childbirth.

Five-Year Plan for Soviet Neurologists The Sixth Five-Year-Plan for the development of clinical neurology in the Soviet Union, as outlined by Grashchenkov, includes: 1) propagandizing of Soviet clinical neurology and the contributions of its chief workers, such as V. M. Bekhterev, L. O. Darkshevitch, and G. I. Rossolimo; 2) organization of a network of institutions for the postgraduate training of clinical neurologists;[2] 3) creation of neurologic departments in general hospitals and of neurologic institutes with special sections in cerebrovascular disease, injuries of the nervous system, neuroinfection, epilepsy, and neurosurgery; 4) improvement in the development of technical instrumentation and more widespread utilization of therapeutic methods; 5) establishment of special problems commissions in cerebrovascular disease, neuroinfection, injuries of the nervous system, brain tumors, and epilepsy; 6) stimulation of scientific societies to provide leadership in all phases of clinical neurology; and 7) maximal broadening of international relations, primarily between Soviet clinical neurologists and neurologists in people's democracies.

Symposium on Cerebellum to Highlight Paris Reunion At its Twenty-second International Neurological Reunion (June 2-4, 1958), the French Society of Neurology will feature a symposium on the cerebellum and, at the same time, will celebrate the centenary of the great French neurologist, J. F. F. Babinski (1857-1932), a student of Charcot, head of the Neurological Clinic at the Hospital de la Pitie (1890-1927), and a founder of the Societe de Neurologie de Paris.... For the coming International Reunion, the French society invites the presence and participation of neurologists from the United States.... The Secretary General of the French Society of Neurology is Dr. Jean Sigwald, 58 Boulevard de Courcelles, Paris 70, France.

Greenfield Died in Bethesda Suddenly, without pain, J. Godwin Greenfield, noted English neurologist and neuropathologist, died of a coronary occlusion while reading in bed on the night of February 28. At the time, he was on his third tour of six months each as a visiting scientist at the National Institute of Neurological Diseases and Blindness, where his presence had become a symbol of clarity and integrity in scientific investigations. At the Institute he was most closely associated

[2]According to this report, as of January 1, 1955, there were in the USSR, 6,044 neurologists and 16,092 persons engaged in neurology—a threefold increase of this specialty since the Fourth Five-Year Plan of 1946.

with the program of G. Milton Shy.... Widely acclaimed as one of the world's leading neuropathologists, Dr. Greenfield was pathologist to the National Hospital, Queen Square, London, from 1914 to 1949. Since 1949 he has dedicated himself entirely to research and writing. He is the author of four major textbooks on diseases of the nervous system, the most recent work being "Muscle Pathology in Neuromuscular Disorders."... Dr. Greenfield was president of the Second International Congress of Neuropathology held in London in September 1955. He was a familiar figure at Academy meetings in recent years, and was scheduled to give the Robert Wartenberg Memorial Lecture at the 1958 annual meeting of the AAN in the Bellevue-Stratford Hotel, Philadelphia (April 24-26).... Dr. Greenfield is survived by his widow, Mrs. Florence Mary Greenfield, a son, two daughters, and six grandchildren, now in England. Mrs. Greenfield, who was at her husband's side at the time of his death, has returned to their home, Garden Hill, Westcott, Dorking, Surrey, England.

Miller Appointed Medical Director of UCP

On February 1, 1958 the appointment of Dr. Brewster S. Miller as medical director of United Cerebral Palsy was announced by Roger S. Firestone, the organization's president. Dr. Miller will also serve as director of United Cerebral Palsy Research and Educational Foundation, which was established in 1955 to expand and strengthen the society's research and training programs.... Formerly administrator for research in therapy of the American Cancer Society, Dr. Miller succeeds Dr. Glidden L. Brooks, who resigned from UCP in 1957 to become director of the Institute of Research in Health Sciences at Brown University, Providence, Rhode Island.

Reese Bailey

You can control tremor

In parkinsonism Parsidol has proved outstandingly effective for controlling tremor and muscular rigidity, the principal impairments in this disease.[1, 2]

With Parsidol most patients show rapid, even dramatic improvement—both in major symptoms and in gait, posture, balance and speech. Side effects are minimal. Parsidol is compatible with all other antiparkinsonian drugs and its effectiveness may even be increased in combination or rotation with such preparations as atropine and dextroamphetamine.[3] Parsidol improves the patient's emotional perspective, promotes a more optimistic outlook as physical coordination and dexterity return.

Most patients can be controlled with a maintenance dosage of 50 mg. four times daily. However, more severe cases may require up to 600 mg. daily, a dosage level ordinarily well tolerated.

References: 1. Doshay, L. J.; Constable, K. and Agate, F. J., Jr.: J.A.M.A. *160*:348 (Feb.) 1956. 2. Berris, H.: J.-Lancet *74*:245 (July) 1954. 3. Timberlake, W. H. and Schwab, R. S.: N. Eng. J. Med. *247*:98 (July 17) 1952.

PARSIDOL®

Brand of ethopropazine hydrochloride

WARNER-CHILCOTT

THE ENCOURAGEMENT OF PROGRESS

The American Cancer Society's annual Spring Crusade is the climax of its year-round attack on cancer through research, professional and lay education, and service to the stricken. A study of the cancer scoreboard indicates that steady progress is being made. More and more lives are being saved. Progress encourages more progress.

Earlier diagnosis, new methods of treatment and a greater public awareness have contributed to this progress. It is often said that the life of the cancer patient is in the hands of the first physician he consults. The Society, therefore, conducts a broad professional education program, making available to doctors, through literature, films, exhibits, and other materials, information on the latest advances in detection, diagnosis and treatment.

As the Society aids the doctor, so does its large corps of volunteers aid the cancer patient with dressings, transportation, home care, medication and a host of other vitally needed services.

For the past two years, the theme of the Society's annual Crusade has been "Fight Cancer with a Checkup and a Check." That Americans everywhere are learning the value of the annual health checkup in the fight against cancer, is evidenced by the fact that doctors report they are now seeing more cancer in its earliest stages than ever before.

That American men and women have a personal stake in the program of the American Cancer Society is demonstrated by the public's generous support of the Crusade. This year the goal is $30,000,000 and we are confident that our people will meet the challenge . . . will "fight cancer with a checkup and a check" in the encouragement of further progress.

Lowell T. Coggeshall, M.D., *President*
American Cancer Society

Founded 1879

RING SANATORIUM

Eight miles from Boston

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. *Courtesy privileges to qualified physicians.*

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts **Telephone MIssion 8-0081**

Accredited by the APA and the Joint Commission on Accreditation of Hospitals

complete integrated facilities for

ELECTROMYOGRAPHY

- **SINGLE CHANNEL EMG** with two-channel magnetic tape recorder for recording notes and EMG simultaneously. — Model TE 1.2-7
- **TWO-CHANNEL EMG** permits simultaneous recording and study of two EMG potentials or of one potential together with a related physical parameter such as force or pressure. — Model TE 2-7

• Automatic controls and new circuits provide simplified reliable operation without shielded rooms in most locations. • EMG potentials faithfully reproduced by special recorder circuits. • Specifications equal or surpass requirements for research, teaching and clinical use.

NEW rugged COAXIAL NEEDLE ELECTRODE withstands autoclaving, has tapered shaft, 26 gauge at tip, insulated handle.

TECA CORPORATION

80 Main St.
White Plains
New York

SPECIFY

GRASS
INSTRUMENTS
FOR
PHYSIOLOGICAL
RESEARCH
AND
CLINICAL
APPLICATION

SHOWN ABOVE

- IT 1 RACKMOUNT INSTRUMENT TABLE.
- C 4 KYMOGRAPH CAMERA.
- S 4 STIMULATORS.
- P 5 A.C. PRE-AMPLIFIERS.
- P 6 D.C. PRE-AMPLIFIER WITH HIGH IMPEDANCE PROBE.
- LS 1 LOUDSPEAKER MONITOR.
- BC 2 BATTERY CHARGER.

OTHER INSTRUMENTS

- SIU 4 STIMULUS ISOLATION UNIT.
- P 7 D.C. HIGH IMPEDANCE PROBE.
- PS 1 PHOTO STIMULATOR.
- FT.03 and FT10 FORCE TRANSDUCERS.
- PT 5 VOLUME TRANSDUCER FOR PLETHYSMOGRAPHY.
- CONTROL CIRCUIT FOR WOOD OXIMETER EAR PIECE.
- CORTICAL and DEPTH ELECTRODES.
- POLYGRAPH, MODEL 5
- ELECTROENCEPHALOGRAPHS, SERIES III AND IV.
- CONVERTERS TO ALLOW TRANSDUCERS AND D.C. POTENTIALS TO RECORD ON MODEL III ELECTROENCEPHALOGRAPHS.

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

Clinical excerpts

Use of meprobamate in chronic psychiatric patients

No. **4** *of a series*

In the treatment of 300 "less promising cases," Miltown produced complete remission of symptoms in 3%, striking improvement in 35%, some improvement in an additional 46%, and no change in 16%.*

*REFERENCE: Pennington, V. M.: Use of Miltown (meprobamate) with psychotic patients. Am. J. Psychiat. 114:257, Sept. 1957.

HOSPITALIZED PATIENTS

DIAGNOSIS	NO. OF PATIENTS	COMPLETE REMISSION	GREATLY IMPROVED	GREATLY IMPROVED OR REMISSION	SOME GAIN	NO CHANGE
Schizophrenia	210	6	69	36%	98	37
Idiopathic epilepsy	16	—	6	38%	10	—
Organic disease	46	—	16	35%	21	9
Involutional, senile, and manic-depressive psychoses	13	2	5	41%	3	3
Anxiety and psychophysiologic reactions, personality disorders	15	1	8	60%	6	—
TOTALS	300	9	104	38%	138	49

Miltown®

• alleviates anxiety in chronic psychiatric patients • facilitates psychotherapeutic rapport • improves disturbed ward behavior • suitable for prolonged therapy • no liver or renal toxicity reported • free of autonomic effects.

The original meprobamate, discovered and introduced by

WALLACE LABORATORIES
New Brunswick, N. J.

a first on the list *

Artane

HYDROCHLORIDE TRIHEXYPHENIDYL HCl LEDERLE

ARTANE is effective in all forms of Parkinsonism, cardiac, hypertensive, postencephalitic and idiopathic types. Well tolerated, ARTANE maintains strong antispasmodic action over prolonged periods of treatment. ARTANE is remarkably free of serious toxic properties, has no deleterious effect on bone marrow function.

Supplied: 2 mg. and 5 mg. tablets, and elixir containing 2 mg. per teaspoonful (5 cc.)

Dosage: 1 mg. the first day, gradually increased, according to response, to 6 mg. to 10 mg. daily divided in 3 doses at mealtime.

*Reg. U.S. Pat. Off.

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK